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The New England Journal of Medicine

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VOLUME 244 · APRIL 26, 1951 · NUMBER 17

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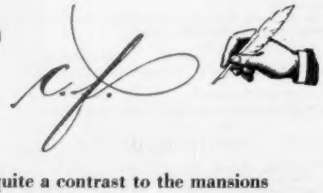

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1. Stokes, J. H.: G. P. 2:33 (Aug.) 1950.
2. Carrier, R. B., Krug, B. S., and Glenn, H. R.: Journal Lancet 68:240 (June) 1948.

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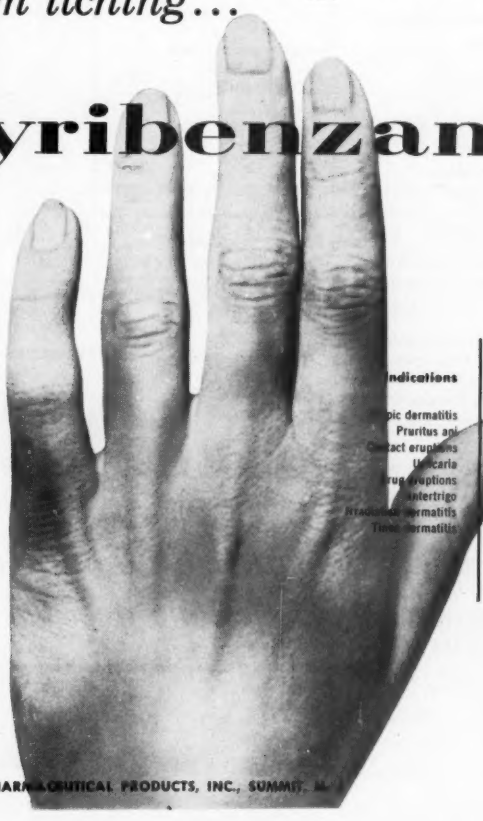

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	A. aerogenes	4	4	0	0
	Aerobic diphtheroids	3	2	1	0
	S. albus	2	2	0	0
	Aerobic non-hemolytic streptococcus	2	2	0	0
	Ps. aeruginosa	1	0	1	0
With organic or obstructive disease					
	Ps. aeruginosa	3	1	0	2
	P. vulgaris	1	0	1	0
	A. aerogenes	1	1	0	0
	TOTALS	32	26	4	2

Douglas, R. G.; Ball, T. L., and Davis, I. F.: California Med. 73:463 (Dec.) 1950

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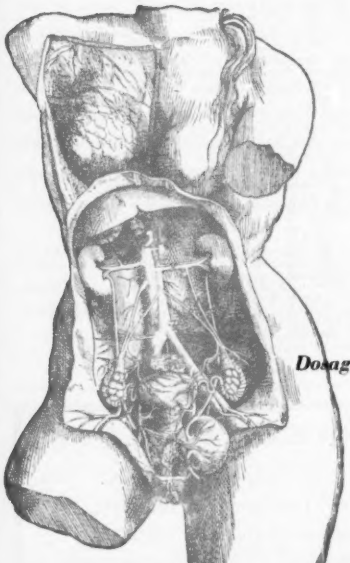

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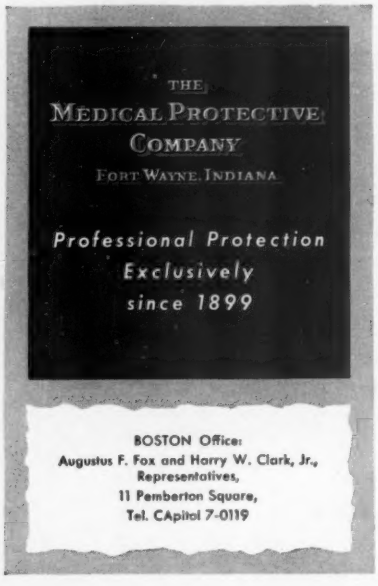

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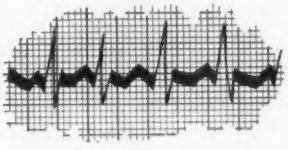

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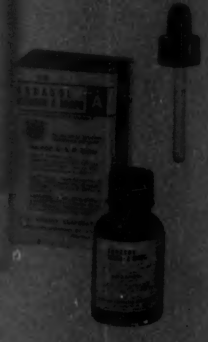

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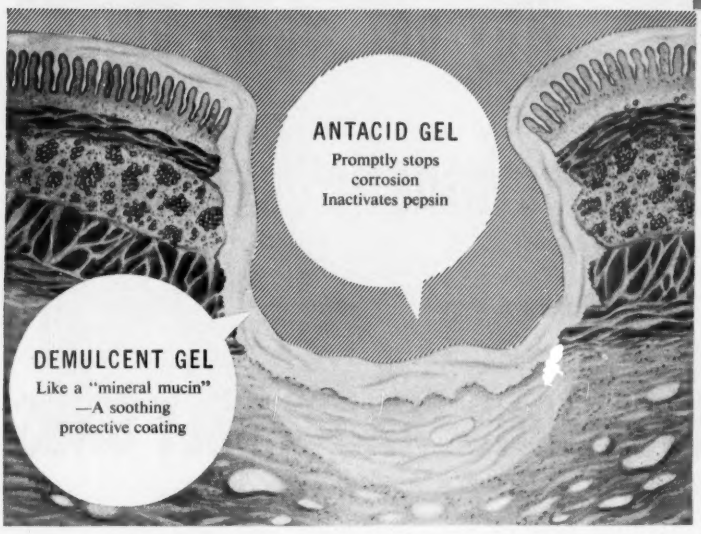

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Lyophilized plasma, for example, can be easily carried anywhere, always ready for immediate use at *five-minute notice* without the need for typing or cross-matching. Because of these advantages, lyophilized plasma has made it possible to save the lives of thousands of desperately injured persons. It is ready for emergencies whenever blood fluids must be immediately replenished, even in extremely unfavorable field conditions in the services and under circumstances that prevail at the scene of disasters in civilian life: at automobile and train wrecks, fires in dwellings, industrial accidents, explosions, storms, and floods.

Whole Blood

In many cases of severe bleeding the *subsequent transfusion of whole blood* is essential for ensuring the complete recovery of the patient. The use of whole blood makes possible the direct restoration of red cells thereby replacing those lost through bleeding. Nevertheless, injection of plasma is a valuable emergency measure, even in acute hemorrhage, because it has been shown that the greatest hazard is not loss of red cells but loss of fluid *volume* and the resultant fall in blood pressure that brings on circulatory failure and tissue anoxia. In such cases, infusion of plasma restores natural blood fluid, increasing the efficiency of the circulation and so promotes delivery of oxygen to the tissues by speeding the travel of those red cells that remain. With only about two million red cells per cubic millimeter of blood, it has been found that oxygenation of the tissues may be maintained if the circulation is adequate. Naturally, the finding of such a low cell count indicates the need for giving whole blood or a suspension of red cells as soon as possible.

Not Plasma *Versus* Blood

In severe burns, excessively large quantities of plasma are often lost, but red cells ordinarily do not escape from the vessels. Consequently whole blood is not usually given in the treatment of burned patients because of the possibility of thickening the blood by adding too many cells. Adequate amounts of plasma alone are urgently needed to restore circulating blood *volume*. There are also certain other uses for which plasma is better suited than whole blood, such as treatment of severe dehydration, traumatic shock, and other conditions in which circulating blood volume is reduced without excessive loss of blood cells.

But Plasma *Plus* Blood

But it should be emphasized that there are many situations in which transfusions of whole blood are indispensable. It would be unintelligent to consider *either* blood *or* plasma as superior to the other *in general*. Circumstances such as the patient's condition, the concentration, volume, and pressure of the blood, as well as the time element will usually determine the choice.

It is not a question of "blood *versus* plasma" but a question of how to utilize "blood *plus* plasma" to best advantage. There are no "substitutes" for either.

It is not a question of "blood versus *plasma" but a question of how to utilize "blood* plus *plasma" to best advantage. There are no "substitutes" for either.*

Plasma "Extenders"

The possibility of a national catastrophe, in which the demand for plasma might suddenly exceed the supply, has led to the search for artificial "plasma extenders" that might be employed as temporary expedients for the emergency treatment of shock.

Recent reports about several such substances that are being used experimentally has focused attention on the mechanical aspects of maintaining the circulation. There is a natural tendency to become preoccupied with the purely *physical* considerations involved in maintaining the fluid volume of the blood and so to exclude—or to give less regard than is due to—vitally important *biological* considerations. The main objective in the search for emergency substitutes for plasma has been to find colloidal materials that could serve to imitate the natural plasma colloids in their ability to increase the osmotic pressure within the blood vessels and so to increase and maintain the amount of fluid they can retain.

Genuine Plasma

Genuine plasma is highly efficient at performing this mechanical osmotic function—but it also does much more. Its natural colloids provide essential nutrients: *protein* for tissue regeneration; many materials necessary for maintaining vital physiologic and metabolic functions; *immune bodies* and *complement*; and substances that maintain the ability of the blood to coagulate. Plasma is the natural, biologically complete, fluid element of human blood.

Popular Misconceptions

To physicians it is obvious that the so-called "plasma extenders" cannot be properly regarded as adequate substitutes for plasma. To the general public, however, the distinction is not entirely clear. A recent news release from the National Research Council points out that it is important to correct popular misconceptions about "blood substitutes." Dr. Winternitz, Chairman of the Council's Division of Medical Sciences, emphasized the fact that, in his opinion, plasma extenders will be for emergency use only. Whole blood and plasma are still absolutely essential. Dr. Winternitz stated that some potential blood donors had received the impression that, since "blood substitutes" were now being made available, it would no longer be important for them to give blood. Dr. Winternitz urged that people with such mistaken notions be correctly informed. It should be made clear that blood donors are still urgently needed—for both military and civilian medicine.

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1. Hutcheson, J. M.: Management of Cardiac Failure. *Virginia Med. Monthly*, 74:458, Oct., 1947.
2. Noth, P. H.: Pick's Disease: A Record of Eight Years' Treatment with Salyrgan, Ammonium Nitrate, and Abdominal Paracentesis. *Proc. Staff Meet. Mayo Clin.*, 12:513, Aug. 18, 1937.

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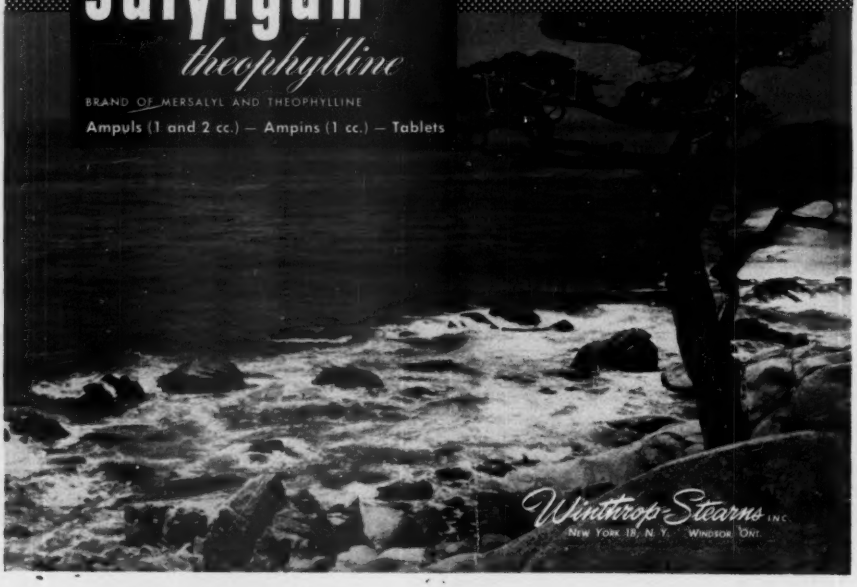

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METABOLIC EFFECTS OF ANESTHESIA IN MAN. IV. A COMPARISON OF THE EFFECTS OF CERTAIN ANESTHETIC AGENTS ON THE NORMAL LIVER*

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BOSTON

THE toxic effects of chloroform on the liver are well known and feared. Studies on animals have suggested a similar role for other anesthetic agents, particularly the ethers. Goldschmidt, Ravdin and Lucké[1] showed that in dogs three hours of anesthesia with divinyl ether or chloroform produced central necrosis of the liver in a large proportion of the animals studied. Diethyl ether produced similar changes, not quite so severe or frequent. The same workers[2] showed the dangers inherent in translation of results from one species to another when they repeated these experiments in monkeys. Here they found histologic changes only with chloroform, and then only when the anesthesia was preceded by a three-day period of starvation, a situation that predisposes to liver damage in the dog or monkey or in man. However, this work in animals is frequently cited as evidence against the use of ether anesthesia in man, especially in cases with liver disease, without taking into account demonstrated species differences.

Previous comparisons in man of the effect of anesthetic agents on liver function are few. In many instances a single test has been used. As we shall point out later, the studies have varied in the care with which they were designed and in their conclusions. Some workers have found no significant difference in the effects of the common anesthetic agents on liver function,[3, 4] whereas others have stated that changes in liver-function test results were less frequent after cyclopropane[5-7] or spinal[8] anesthesia, or more frequent after tribromoethanol (Avertin) anesthesia.[9]

In view of the above discrepant results, the present study was planned in an effort to compare the effects on human liver function of similar operations performed under ether, cyclopropane and spinal anesthesia. The groups of cases have been carefully balanced by preoperative selection in an effort to make the anesthetic agent the chief variable in this complex human experiment. A battery of liver-function tests has been employed, which will be described in detail. It is the purpose of this study to establish the effects of these anesthetic agents on liver function in patients with normal livers. Later we shall compare in a similar way the effects of the same agents in patients with liver disease.

Clinical Material and Methods

The cases selected for study met the following criteria: The age limits were 17 to 65, inclusive. The liver was not enlarged on physical examination. There was no history or physical evidence of gall-bladder disease, hepatitis, jaundice, diabetes, thyrotoxicosis or syphilis. There was no history of an excessive intake of alcohol. The nutritional status was good. There was no evidence of current infection of any sort. The retention of bromsulfalein forty-five minutes after a dose of 5 mg. per kg. of body weight had been administered was 5 per cent or less.

Types of Operation

As Table 1 shows, herniorrhaphies, vein strippings and major pelvic operations were chosen in order to avoid operative trauma to the liver and biliary tract as a complicating factor. An effort was made to balance the series for each type of anesthesia with approximately the same number of each type of operation and with operations of similar duration. Except for one case of carcinoma in situ of the cervix, no malignant lesions were in-

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cluded. When postoperative infection developed before completion of the tests the case was excluded from this series.

Liver-Function Tests

The battery of liver-function tests was performed before operation and on the first, third and fifth postoperative days. The following tests were used:

Bromsulfalein test. Five mg. per kg. of body weight was administered intravenously. The blood specimen was drawn forty-five minutes after injection of the dye. For a given patient the same amount of dye was injected each day on which the test was performed. Dye retention was determined photoelectrically by the method of Gaebler.[10] The accepted normal is not more than 5 per cent dye retention.

Intravenous hippuric-acid test. The injection of 1.77 gm. of sodium benzoate was made intravenously in 20 cc. of water and a urine specimen collected one hour after injection.[11] Hippuric-acid excretion was determined by the precipitation method, using sodium chloride.[12] The accepted normal is 1.0 gm. or more of hippuric acid excreted in one hour. All results are recorded as hippuric acid (not as benzoic acid). The urea clearance performed according to the method of Peters and Van Slyke[13] was used as a screening test to exclude those cases in which an unsuspected reduction of renal function would invalidate the hippuric-acid test. The urea clearance actually proved too sensitive a test for this purpose. The phenolsulfonphthalein test of kidney function could not be used because of the simultaneous injection of bromsulfalein.

Serum bilirubin. The method of Malloy and Evelyn[14] was used. All figures represent the total serum bilirubin. The commonly accepted upper limit of normal is 0.7 mg. per 100 cc.

Plasma prothrombin time. The method of Quick[15] was used. All results are recorded as the number of seconds by which the patient's prothrombin time exceeded that of the control. Control figures

TABLE 1.

Case No.	Sex	Operation	Duration of Operation	Age	Bromsulfalein Retention				Hippuric-Acid Excretion			
					Pre-operative day	First	Third	Fifth	Pre-operative day	First	Third	Fifth
					%				1 hr.			
Gas-Oxygen-Ether												
11	F	Abdominal hysterectomy	4:20	44	1	1	2	1	0.5	0.2	0.4	0.9
15	F	Abdominal hysterectomy	3:00	37	2	1	1	14	0.5	0.7	0.4	1.5
18	F	Abdominal hysterectomy	2:35	39	1	1	0	3	1.0	—	0.6	0.4
73	F	Abdominal hysterectomy	5:40	45	4	8	23	9	—	—	—	—
29	F	Vaginal hysterectomy	2:25	57	4	2	6	2	1.4	0.3	0.5	1.1
16	F	Varicose-vein stripping	1:30	55	2	1	4	—	0.8	1.1	0.7	—
32	F	Varicose-vein stripping	3:20	41	4	14	6	—	0.8	—	1.2	—
36	F	Varicose-vein stripping	3:30	43	4	5	5	—	1.3	1.6	1.5	—
41	M	Varicose-vein stripping	4:30	35	1	2	0	—	1.6	1.4	1.2	—
42	F	Varicose-vein stripping	5:07	39	1	2	3	—	1.1	1.2	0.9	—
17	M	Hernia	2:40	41	5	18	12	10	—	0.8	0.9	0.9
34	M	Hernia	1:50	56	5	7	3	—	1.0	1.3	1.1	—
72	F	Hernia	3:15	40	2	11	5	3	—	—	—	—
Average ...			3.1	44	2.8	5.6	5.4	6.0	1.00	0.95	0.85	0.96
Standard error of mean (±)					0.44	1.57	1.71	1.88	0.12	0.16	0.11	0.18
Cyclopropane												
38	F	Abdominal hysterectomy	2:15	47	5	10	32	26	0.8	0.1	1.0	0.8
46	F	Abdominal hysterectomy	3:40	47	2	1	1	2	1.2	1.0	0.6	—
48	F	Abdominal hysterectomy	2:15	28	2	7	3	2	0.9	1.0	0.9	1.1
33	F	Vaginal hysterectomy	1:55	61	3	—	—	3	0.8	1.1	1.2	1.1
12	F	Varicose-vein stripping	2:28	52	1	3	2	2	1.2	0.2	1.1	1.3
23	F	Varicose-vein stripping	0:50	44	3	14	10	—	0.4	1.0	1.1	—
24	F	Varicose-vein stripping	1:00	59	2	19	5	—	0.2	—	1.1	—
25	F	Varicose-vein stripping	3:25	38	1	1	1	—	1.5	1.3	1.4	—
4	M	Hernia	3:10	60	1	4	0	—	1.5	—	—	—
31	M	Hernia	2:40	49	1	2	0	—	1.0	0.9	1.1	—
75	F	Uterine suspension	1:40	20	2	8	7	4	—	—	—	—
Average ...			2.3	46	2.1	6.9	6.1	6.5	0.95	0.82	1.06	1.07
Standard error of mean (±)					0.37	1.90	3.06	3.91	0.14	0.15	0.07	0.10
Spinal												
5	F	Vaginal hysterectomy	1:55	62	1	2	3	3	1.3	0.7	1.0	0.7
6	F	Vaginal hysterectomy	2:33	44	0	1	2	2	1.3	1.5	1.1	1.2
54	F	Vaginal hysterectomy	2:10	53	3	6	8	3	0.4	0.7	1.2	0.8
50	F	Perineal repair	2:10	55	2	9	11	9	1.1	1.1	0.1	0.9
67	F	Perineal repair	1:40	56	4	8	9	5	0.8	0.8	—	1.3
45	M	Hernia	2:55	19	3	4	3	2	0.7	—	—	—
47	M	Hernia	2:00	31	1	6	1	—	—	—	0.5	—
62	M	Hernia	1:45	58	4	19	3	—	0.7	1.1	1.1	—
88	M	Hernia	1:35	30	2	4	2	2	—	—	—	—
94	M	Hernia	2:15	60	5	3	8	—	0.9	1.4	—	—
Average ...			2.1	47	2.5	6.2	5.0	3.8	0.90	1.04	0.83	0.98
Standard error of mean (±)					0.51	1.63	1.14	0.96	0.11	0.12	0.18	0.12

*Bodansky units.

for prothrombin time in all but one instance fell between fourteen and eighteen seconds.

Urine urobilinogen. This was determined on a two-hour specimen of urine by the method of Watson, Schwartz, Sborov and Bertie.[16] The accepted normal is not more than 1.0 Ehrlich unit in two hours.

Serum alkaline phosphatase. The method of Bodansky[17] was used. The accepted upper limit of normal is 4.5 units per 100 cc.

falein was injected through the same needle and the time recorded. A blood specimen was drawn forty-five minutes after the bromsulfalein injection for all chemical determinations, including the urea level for urea-clearance calculation. A urine specimen was collected one hour after the injection of the sodium benzoate. This specimen was used for the hippuric-acid determination and also as the first urea-clearance specimen. A timed urine specimen was collected approximately two hours

TABLE 1 (*Concluded*).

Case No.	Serum Bilirubin				Prolongation of Plasma Prothrombin Time				Urine Urobilinogen				Serum Alkaline Phosphatase				Cholesterol Esters			
	Pre-operative day	First	Third	Fifth	Pre-operative day	First	Third	Fifth	Pre-operative day	First	Third	Fifth	Pre-operative day	First	Third	Fifth	Pre-operative day	First	Third	Fifth
	mg./100 cc.				sec.				units/2 hr.				units/100 cc.				% of total cholesterol			
Gas-Oxygen-Ether																				
11	1.0	0.7	0.8	0.4	0	1	4	5	0.4	0.5	0.9	0.7	1.4	2.0	1.5	1.7	—	—	—	—
15	0.9	1.2	0.5	0.5	1	1	0	0	0.5	1.9	1.1	1.0	—	1.6	2.0	5.0	69	—	59	—
18	0.4	0.6	0.5	0.5	0	4	0	2	0.3	—	0.4	—	1.2	0.9	—	2.1	70	56	52	69
73	0.6	0.6	0.2	0.4	0	2	3	4	0.4	0.2	1.1	—	1.8	2.3	2.4	2.0	—	—	—	—
29	0.7	0.9	0.4	1.2	0	1	0	0	0.5	0.7	0.3	1.5	2.0	2.8	1.5	1.9	71	56	35	40
16	0.6	0.9	0.5	—	0	0	0	—	0.5	0.6	0.7	—	1.8	1.9	3.7	—	70	54	45	—
32	0.4	0.5	0.4	—	3	3	7	—	0.1	—	0.3	—	—	—	—	—	64	58	48	—
36	0.7	0.7	1.4	—	0	1	2	—	0.3	1.0	0.4	—	1.8	2.1	3.3	—	—	53	52	—
41	1.0	0.7	0.6	—	2	2	4	—	0.7	1.5	0.5	—	—	—	—	—	55	65	60	—
42	0.6	0.7	0.6	—	1	13	0	—	0.6	0.4	0.6	—	—	—	—	—	58	57	—	—
17	0.5	0.6	0.5	0.5	0	0	8	5	0.5	0.9	0.7	0.3	4.0	1.8	4.0	4.5	57	52	—	50
34	0.6	0.4	0.4	—	1	4	4	—	0.4	0.5	0.5	—	—	—	—	—	58	59	62	—
72	1.0	1.0	0.9	0.3	0	3	0	2	0.2	0.6	1.4	0.7	2.0	1.8	1.8	2.2	—	—	—	—
	0.69	0.73	0.59	0.54	0.6	2.7	2.5	2.6	0.41	0.80	0.68	0.84	2.0	1.9	2.5	2.8	61	57	52	53
	0.06	0.06	0.08	0.11	0.27	0.94	0.78	0.82	0.04	0.15	0.10	0.19	0.30	0.17	0.36	0.52	3.7	1.3	3.2	8.5
Cyclopropane																				
38	1.0	1.2	0.8	0.6	1	1	1	2	0.6	1.3	2.7	1.9	1.5	1.2	1.7	2.1	59	50	51	39
46	0.6	0.5	0.5	0.6	2	3	0	2	0.6	0.3	0.6	1.9	—	—	—	—	27	56	55	53
48	0.4	0.4	0.4	0.4	3	2	2	2	0.2	—	1.8	0.9	—	—	—	—	66	50	53	51
33	0.8	0.9	0.3	0.4	0	2	5	—	0.7	0.4	0.3	0.1	2.5	1.0	3.0	1.7	55	73	62	—
12	1.2	1.2	1.0	0.7	0	0	1	1	0.5	0.2	0.4	0.3	2.6	2.1	2.3	1.7	—	—	—	—
23	0.5	1.3	0.5	—	3	2	6	—	0.4	0.8	0.4	—	2.7	3.4	2.7	—	65	66	64	—
24	0.9	1.7	0.5	—	0	1	0	—	0.4	—	0.4	—	1.9	1.4	2.4	—	43	63	61	—
25	1.2	0.6	0.8	—	0	2	0	—	0.3	0.4	0.3	—	1.7	3.4	2.8	—	49	45	36	—
4	0.8	0.7	0.8	—	1	0	—	—	0.8	2.5	1.0	—	4.8	2.1	—	—	—	—	—	—
31	0.4	0.4	0.5	—	3	1	4	—	0.8	1.1	0.5	—	1.5	1.3	1.7	—	64	56	57	—
75	0.7	0.5	0.2	0.3	0	2	3	3	—	1.6	0.1	0.7	2.0	1.3	1.8	1.8	—	—	—	—
	0.77	0.85	0.57	0.50	1.2	1.4	2.2	2.0	0.53	0.96	0.77	0.97	2.4	1.9	2.3	1.8	53	57	55	48
	0.09	0.13	0.07	0.06	0.40	0.29	0.70	0.32	0.06	0.25	0.24	0.32	0.34	0.31	0.19	0.10	4.8	5.3	3.1	4.4
Spinal																				
5	0.5	0.5	0.5	0.5	1	0	1	1	0.4	0.3	0.3	0.3	3.3	1.9	2.4	3.5	—	—	—	—
6	0.5	0.4	0.4	0.4	0	0	1	3	1.2	0.6	0.6	0.2	2.1	1.1	0.8	1.3	—	—	—	—
54	2.5	2.2	0.6	0.7	1	5	3	3	0.5	0.4	0.6	1.6	—	—	—	—	66	63	61	60
50	1.9	1.8	0.9	0.6	1	0	0	0	0.3	0.8	—	1.9	—	—	—	—	60	48	80	71
67	0.5	1.0	0.8	0.6	0	2	3	1	0.7	0.4	0.8	1.8	3.3	4.6	3.5	2.9	68	61	62	66
45	0.9	0.5	0.7	0.6	4	3	5	3	0.6	—	—	—	—	3.1	—	—	52	51	39	42
47	1.2	1.0	0.6	—	2	2	3	—	—	—	—	—	—	—	—	—	48	44	52	—
62	—	0.7	0.4	—	2	5	3	—	0.6	0.8	0.5	—	2.8	2.8	2.0	—	55	59	61	—
88	1.2	1.6	0.9	0.7	2	1	0	2	—	0.8	—	2.9	1.0	1.4	1.7	1.3	—	—	—	—
94	0.7	0.6	0.4	—	0	0	—	—	0.3	0.4	0.9	—	3.9	3.3	4.3	—	67	60	—	—
	1.10	1.03	0.62	0.59	1.3	1.8	2.1	1.9	0.57	0.56	0.62	1.45	2.7	2.6	2.5	2.2	59	57	59	60
	0.23	0.20	0.05	0.04	0.39	0.63	0.56	0.46	0.10	0.08	0.09	0.42	0.43	0.46	0.52	0.56	3.0	2.8	5.5	6.4

Serum cholesterol and cholesterol esters. The method of Bloor[18, 19] was used. All figures represent the percentage of cholesterol present as cholesterol esters. The accepted normal is approximately 65 per cent of esters.

Procedure

The tests were performed in a fixed routine: The patient voided. This marked the start of the first urea-clearance period. The sodium benzoate was injected; time was again observed. The bromsulfalein was injected through the same needle and the time recorded. A blood specimen was drawn forty-five minutes after the bromsulfalein injection for all chemical determinations, including the urea level for urea-clearance calculation. A urine specimen was collected one hour after the injection of the sodium benzoate. This specimen was used for the hippuric-acid determination and also as the first urea-clearance specimen. A timed urine specimen was collected approximately two hours after the first. This was used for the urobilinogen determination and also for the second urea-clearance specimen. The majority of urobilinogen specimens were collected between approximately 10 a.m. and noon.

Urine specimens could not be obtained on some days following operation, owing to the patient's inability to void satisfactorily. A few results are lacking because of technical accidents. A number of patients were discharged from the hospital before time for the fifth-day postoperative tests. These

variations from the established plan are evident in Table 1. Those patients in whom the fifth-day tests could not be done are included in the series because, in the series as a whole, all but two of the patients who showed postoperative impairment of liver function showed this impairment by the first or third postoperative day. In all but one of these "normal" patients the abnormal bromsulfalein retention was decreasing rather than progressing on the fifth day.

Five patients were discarded from the normal series because of postoperative infection. This was shown in all cases by sustained fever over 101°F.

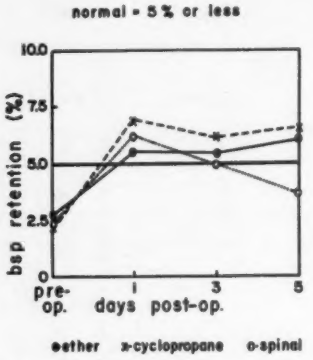

FIGURE 1. *Average Bromsulfalein Retention.*

and in all but one case by evidence of localized infection. These cases, as well as those discarded from the present series because of the preoperative finding of liver disease or liver-function abnormalities, will be discussed in a subsequent report.

RESULTS

The results of the tests are shown in Table 1. The preoperative test is listed first, followed by the findings on the first, third and fifth days after operation. More than half the cases in each anesthesia group showed an increase in bromsulfalein retention to above normal at some point postoperatively. Almost every case showed abnormal findings in at least one of the tests during the study. The averages of the results in each anesthesia group are shown, with the standard error of the mean listed below the average.

Bromsulfalein test. As Figure 1 demonstrates, the averages show no significant difference among the groups of patients who received ether, cyclopropane and spinal anesthesia. Seven of 13 ether cases, 6 of 11 cyclopropane and 6 of 10 spinal-anesthesia cases showed abnormal postoperative bromsulfalein retention. Five of 13 ether, 4 of 11 cyclopropane and 2 of 10 spinal-anesthesia cases attained bromsulfalein retentions of over 10 per cent. On the fifth postoperative day 3 ether cases showed abnormal and 4 showed normal bromsulfalein retention. The cyclopropane cases on this day included 1 with abnormal and 5 with normal bromsulfalein retention. In the spinal-anesthesia cases 1 showed abnormal and 6 normal bromsulfalein retention on the fifth postoperative day. These differences are not statistically significant, but it is conceivable that more data might show more frequent abnormalities on the fifth day after operation with ether than with the other two agents.

It will be seen in Table 1 that the results of the bromsulfalein test in any one case consistently follow a smooth curve, with the peak elevation on the first or third postoperative day (one exception). This confirms the reliability of the bromsulfalein test, which is by far the most valuable of those used in the present study.

Hippuric-acid test. It will be seen that results of this test were often abnormal before operation. Analysis of the cases in which hippuric-acid excretion was less than 1.0 gm. before operation has shown that an abnormal preoperative level did not predispose to postoperative abnormalities in the other tests, or even to abnormalities in the postoperative hippuric-acid tests. There are numerous cases in which an initially low hippuric-acid excretion was followed by rising excretion in all the postoperative tests, and in 5 cases all the postoperative tests were normal after a low preoperative test. We consider that these irregularities, with the failure of hippuric-acid excretion to parallel other tests, make this test less valuable than others. The averages (Fig. 2) show no significant changes either after operation or between anesthetic agents. Once with each anesthetic agent there was a striking drop

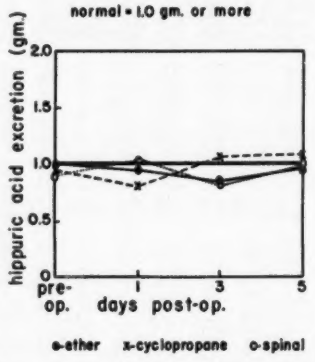

FIGURE 2. *Average Hippuric-Acid Excretion.*

in hippuric-acid excretion from normal levels to 0.3 gm. or less (Cases 11, 12, 50). The level in one other patient who received cyclopropane anesthesia fell from 0.8 gm. to 0.1 gm. excretion.

Serum bilirubin. These normal cases did not show much change in the serum bilirubin (Fig. 3). It was common to find a preoperative bilirubin

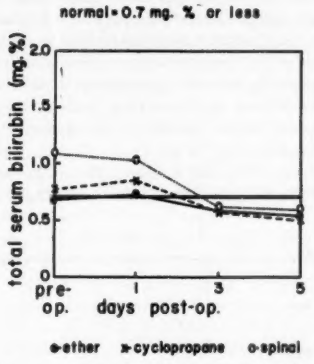

FIGURE 3. *Average Total Serum Bilirubin.*

level above the accepted normal (45 per cent of cases). This tended to remain steady on the first postoperative day and then, in most cases, became normal for the rest of the study. A preoperative elevation in serum-bilirubin level did not predis-

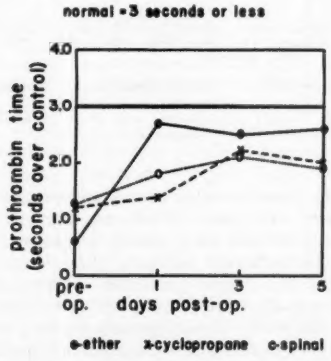

FIGURE 4. *Average Increase in Prothrombin Time.*

pose to postoperative abnormalities in the serum bilirubin or other tests.

Prothrombin. The changes in the prothrombin level in normal cases were neither frequent nor striking (Fig. 4). Although they were not statistically significant, there was a higher percentage of abnormal results with ether anesthesia than with either cyclopropane or spinal anesthesia. With ether anesthesia 8 of 13 cases showed prolongation of prothrombin time of more than three seconds, whereas with cyclopropane and spinal anesthesia this occurred 3 times with each agent.

Urobilinogen. Although not many cases showed a marked rise in urine urobilinogen, values above normal did occur postoperatively in 5 of 13 ether-

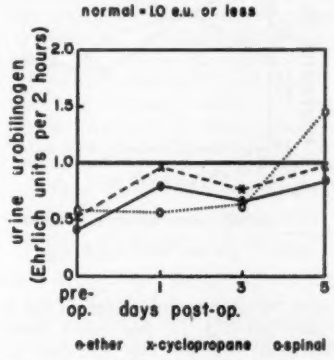

FIGURE 5. *Average Urine-Urobilinogen Excretion.*

anesthesia cases, 6 of 11 cyclopropane cases and 4 of 10 spinal-anesthesia cases. In general the rise was on the first or third postoperative day, but the spinal-anesthesia cases showed little rise in the early

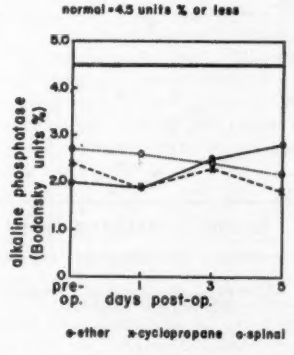

FIGURE 6. *Average Serum Alkaline Phosphatase.*

days, with a distinct rise on the fifth postoperative day (Fig. 5).

Serum alkaline phosphatase. There were no significant changes in the serum alkaline phosphatase in these normal subjects after operation (Fig. 6).

Cholesterol. The ratio of cholesterol esters to total cholesterol varied considerably, and the variation is so large that differences between anesthetic groups or postoperative trends, if any, are masked. The data for the fifth day are so small that they have

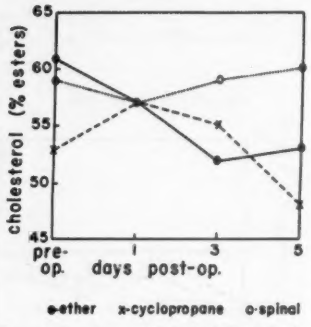

FIGURE 7. *Average Cholesterol-Ester Ratio.*

little value, but they are included in the averages for completeness (Fig. 7). Individual cases showed wide variations, and two cases rose from quite low

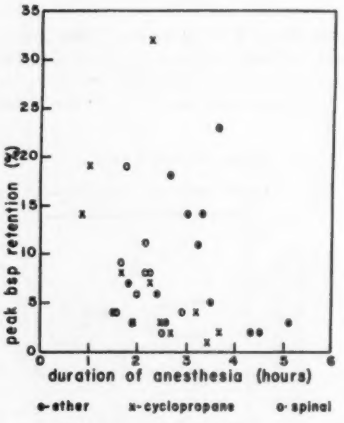

FIGURE 8. *Duration of Anesthesia as Compared with Peak Bromsulfalein Retention.*

preoperative levels to normal levels throughout the postoperative period.

DISCUSSION

The observations in these cases show, as others have shown before, that in normal persons there is alteration in liver-function tests after operations. This alteration is sometimes striking. The present study was planned to observe the effect of one factor, anesthesia, in this complex equation. In our plan we have tried to control a number of variables:

Type of operation. All operations were on the legs or lower abdomen; the proportion of each type of operation is roughly the same in each anesthesia group, except that the spinal anesthesia group contains more herniorrhaphies and no vein strippings, since the latter operation is usually too long for single-shot spinal anesthesia. The results of Zamcheck, Chalmers and Davidson[20] suggest that upper-abdominal operations show more frequent variations from normal, but in these cases there is the added possibility of operative trauma to the liver or bile ducts.

Duration. As Table 1 shows, the ether-anesthesia cases were of somewhat longer average duration

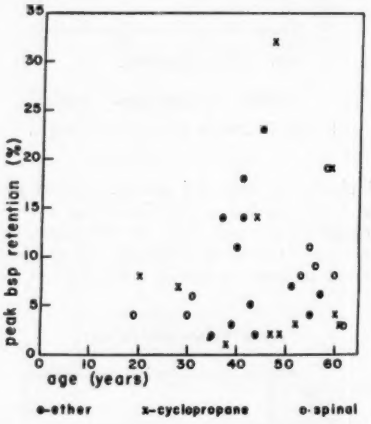

FIGURE 9. *Age as Compared with Peak Bromsulfalein Retention.*

than the cases in which cyclopropane and spinal anesthesia were used. When the duration of anesthesia is plotted on a scatter graph against the rise in bromsulfalein retention (Fig. 8), it is evident that there is no correlation of bromsulfalein-test abnormality with duration of operation in this series. Only two of our operations lasted an hour or less; even in these cases the peaks of bromsulfalein retention were 14 per cent and 19 per cent.

Age. The ages are well balanced, with averages at 44 for the patients who received ether, 46 for those who received cyclopropane and 47 for the spinal-anesthesia cases. Rafsky and Newman[21] described impaired liver function in the aged, and Coleman[9] considered age to be an important factor in his study of liver function after anesthesia. Figure 9 shows age in decades plotted against the

peak of bromsulfalein retention. It is seen that there is no significant correlation. Since the average ages in the different anesthesia series are so close, and since we can find no correlation between age and abnormality of liver-function tests, we conclude that age is not a factor in any difference among these series.

Anoxia. The work of Goldschmidt, Ravdin and Luckè[1] demonstrates that in dogs anoxia alone can cause liver damage and that anoxia aggravates the damage caused by anesthetic agents in dogs. In the present series the trained anesthetists who cared for the patients were aware of the dangers of anoxia and took particular care to exclude it as a variable in the present study. Careful notes were kept during the operation; anoxia was not present in any of these patients.

Shock. Shock was not present in any of the patients in this series.

Nutrition. All procedures included in this study were elective operations on patients who were on a normal diet up to the time of operation. After operation most of the patients were given an intravenous injection of 1500 to 3000 cc. of a 5 per cent solution of dextrose in distilled water and took nutrient liquids orally by the second or third postoperative day, followed by soft foods for a day or two after that.

Infection. Postoperative infection, as mentioned above, occasioned the exclusion of such a patient from this series. We have found, as did Keeton,[22] and contrary to the observations of Coleman,[9] that the presence of any infection, in the wound or elsewhere, causes increased abnormality of the test results.

Preoperative liver abnormality. Little is known about the borderlines of functional capacity between "normal" and "abnormal" livers. When we separated the cases with a preoperative bromsulfalein retention of 4 or 5 per cent from those with an initial retention of less than 4 per cent, it was seen that these cases with an initial retention of 4 to 5 per cent showed greater and more frequent postoperative retention of bromsulfalein. Of 10 cases with a preoperative bromsulfalein retention of 4 or 5 per cent 9 (90 per cent) showed abnormal bromsulfalein retention after operation, whereas of 24 cases with bromsulfalein retention of less than 4 per cent before operation only 9 (38 per cent) became abnormal after operation. This increased frequency of postoperative abnormality of liver function in patients with preoperative bromsulfalein retention of 4 or 5 per cent was also reflected in the other tests of these patients. We have studied the cases that show preoperative "abnormalities" in the hippuric-acid test or in serum bilirubin, and we find that they show statistically no consistent increase in postoperative abnormalities, either in the test involved or in the other tests. We believe that bromsulfalein retention is the most helpful of all these tests, particularly in predicting how the liver will react to this type of stress.

Effect of anesthetic agent. There was a striking lack of difference among the series of patients who received ether, cyclopropane or spinal anesthesia. The small differences that did appear were nowhere statistically significant.

We conclude, as did Coleman[9] in his experience with the bromsulfalein test, that there is no significant difference between gas-oxygen-ether anesthesia and spinal anesthesia. His one case in which ether was given by the open-drop method showed bromsulfalein retention after operation. Unfortunately, the data in his report do not include the degree of retention. Three of our ether patients received open-drop ether anesthesia; one showed no postoperative abnormalities, and the changes in the other two cases were slightly less than average. We doubt that there is any difference in the effects on liver function between these methods of administration of ether. Coleman found an increased frequency of change with tribromoethanol (Avertin) anesthesia.

Boyce and McFetridge,[3] using the oral hippuric-acid test, found that ether and spinal anesthesia caused similar degrees of liver dysfunction initially and that the spinal-anesthesia cases returned sooner toward normal. In our series this late trend of the spinal-anesthesia cases was not present in the hippuric-acid test, and in the bromsulfalein test it was not of significant degree. With regard to urobilinogen excretion, there were more late abnormalities with spinal than with the other types of anesthesia.

Schmidt, Unruh and Chesky[8] also used the oral hippuric-acid test. They expressed the idea that in many persons with apparently normal livers the reserves are "distressingly limited" when an added burden is placed on this organ. They reported changes in all cases of a mixed series of operations under ether anesthesia. They found changes with spinal anesthesia only if shock was present, but we found frequent changes with spinal anesthesia. Shock was present in none of our cases.

Engstrand and Friberg[5] used the intravenous hippuric-acid test. They observed the effect of shock in aggravating the changes, and said: "Cyclopropane appears to affect liver function only to a slight extent, even in cases where there is considerable injury to the liver." Their tables contain full results of their tests (one of the few reports that do so) and we believe that the data, which are not controlled by comparable studies with other agents, do not warrant the conclusion that cyclopropane is preferable to other agents in cases with liver damage. In our series the changes in bromsulfalein retention, as well as in the other liver-function tests, are as great with cyclopropane as with the other anesthetic agents. Furthermore, a study parallel to the present one (to be reported

later) has shown that in patients with severely damaged livers the changes in liver function after operation show no difference between ether and cyclopropane anesthesia.

Pohle[4] compared the effects of six anesthetic agents on liver-function tests, including icteric index, cephalin-cholesterol flocculation, bromsulfalein retention and prothrombin time. He states that "impairment of liver function was observed in approximately 50 per cent of the cases, irrespective of which anesthetic agent had been administered." He used chloroform, ether, cyclopropane, spinal, Pentothal and tribromoethanol (Avertin) anesthesia, hence his results disagree with those of Coleman[9] with respect to this last agent and with Engstrand and Friberg's[5] conclusions concerning cyclopropane. In Pohle's series, chloroform shows an incidence of changes no greater than the other anesthetic agents. The data that he presents deal only with the frequency of abnormal values and do not mention the degrees of abnormality. His patients were not normal, since most had malignant disease and were poorly nourished; the variety of operations introduced another variable into this series. We have tried to reduce the number of these variables, and have reached the same conclusion: that the effect on the normal liver of the anesthetic agents studied is essentially the same.

Mechanism of changes. The group of patients who were operated on under spinal anesthesia was originally included with the thought that it would serve as a control, against which the "toxic effects" of the other two agents could be compared. The fact that there were no significant differences in the changes observed with the different types of anesthesia indicates to us that the anesthetic agent is probably not the significant factor in producing these changes. Additional evidence against a toxic etiology for these changes is the fact that duration of exposure to the agent showed no correlation with the degree or frequency of the changes. These changes evidently represented the effect on the liver of the total stress situation attendant on operation. This is supported by studies that we have begun on the effect of infections, which have consistently been followed by increased abnormality of the liver-function tests.

Summary and Conclusions

A battery of liver-function tests was performed before anesthesia and on the first, third and fifth days after operation in 34 patients who underwent operations on the lower abdomen and legs. The patients had neither history nor clinical evidence of liver disease or other systemic disease. None had a preoperative bromsulfalein retention of over 5 per cent. An effort was made to eliminate all variables except the anesthetic agent by balancing the series for age, duration and types of operation and by avoiding shock, anoxia and malnutrition.

Abnormalities were present after operation in almost every case. The bromsulfalein retention was the most useful test. It was elevated in 18 of the 34 cases at some point in the postoperative period, at times reaching 15 to 30 per cent retention.

There was a striking lack of correlation between duration of anesthesia and incidence of abnormal liver function.

We conclude that there is no significant difference in ether, cyclopropane and spinal anesthesia in their effect on the normal human liver.

It is probable that the changes in liver function observed represent a part of the organism's total reaction to stress rather than a toxic effect of the anesthetic agents employed.

We are indebted to Professor Frederick Mosteller of the Department of Social Relations of Harvard University for helpful advice and a careful statistical analysis of this study. We also wish to thank Mrs. Jean Sears, Miss Heather Cockfield and Miss Margaret Rourke for their technical assistance.

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THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH AUREOMYCIN AND CHLOROMYCETIN*

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PRIOR to the introduction of penicillin subacute bacterial endocarditis was nearly always fatal. In the past five years the many reports that have appeared on penicillin therapy of this infection a rate of cure of 72 per cent.[1] Those cases of subacute bacterial endocarditis in which the etiologic bacterium was *Streptococcus viridans* have yielded most readily to penicillin.[2, 3] However, *Streptococcus*

TABLE 1. *Results of Antibiotic Therapy in 11 Cases of Subacute Bacterial Endocarditis.*

Case No.	Age	Sex	Duration of Illness	Infecting Organism	Therapy				Remarks
					Antibiotic*	Daily dose†	Duration days	Results	
1	55	M	4 mo.	*Str. faecalis*	Aureomycin	4 gm.	8	Failure	Blood cultures remained positive prior to administration of penicillin (12,000,000 units daily). Patient died in congestive failure 37 days after therapy was discontinued.
					Aureomycin + penicillin	4 gm. 2,000,000 units	2	Failure	
					Aureomycin + penicillin	4 gm. 12,000,000 units	17		
					Penicillin	12,000,000 units	14	Cure	
2	64	M	8 mo.	*Str. faecalis*	Penicillin	8,000,000 units	30	Failure	Patient remained afebrile but died in congestive failure 60 days after withdrawal of antibiotic therapy.
					Aureomycin	4 gm.	14	Failure	
					Penicillin + caronamide	8,000,000 units 24 gm.	42	Cure	
3	49	M	1 yr.	*Str. faecalis*	Aureomycin	2–4 gm.	8	Failure	After 7th day of aureomycin therapy *A. aerogenes* could be cultured consistently from the blood. Patient died.
					Streptomycin	0.5–2 gm.	3	Failure	
					Streptomycin + penicillin	3 gm. 800,000 units	5	Failure	
4	51	M	3 mo.	*Str. viridans*	Aureomycin	4 gm.	17		Patient well 11 mo. after treatment
					Penicillin	1,000,000 units	7	Cure	
5	66	F	3 mo.	*Str. viridans*	Aureomycin	4–6 gm.	34	Cure	Patient well 12 mo. after treatment
6	21	F	4 wk.	*Str. viridans*	Chloromycetin	4 gm.	35	Cure	Patient well 5 mo. after treatment
7	47	M	10 mo.	*Str. viridans*	Chloromycetin	4 gm.	21	?	Patient died in congestive failure during treatment
8	53	M	3 mo.	*Str. viridans*	Chloromycetin	4 gm.	14	Failure	Patient relapsed 2 days after withdrawal of Chloromycetin. Well 4 mo. after penicillin therapy.
					Chloromycetin	3 gm.	21		
					Penicillin	2,000,000 units	42	Cure	
9	27	F	17 days	*Staph. aureus*	Penicillin	6,000,000 units	3	Failure	*Alcaligenes faecalis* isolated from blood cultures on the 10th, 11th, 12th and 16th days of combined penicillin and Chloromycetin therapy. Patient died.
					Penicillin + Chloromycetin	6,000,000 units 6 gm.	19	Failure	
					Aureomycin	1.0 gm. intravenously 0.5 gm. orally	10	Failure	
					Aureomycin	2 gm.	3	Failure	
10	41	F	4½ mo.	*E. coli*	Gantrisin	6 gm.	7	Failure	Patient's temperature normal within 24 hours after neomycin therapy. Blood cultures sterile for 6 days, at the end of which time she died as result of cerebral embolus.
					Aureomycin	400 mg. intravenously 2 gm. orally	7	Failure	
					Terramycin	2.5 gm.	5	Failure	
					Streptomycin	3–4 gm.	19	Failure	
					Neomycin	2 gm.	5	?	
11	53	F	2½ mo.	Unknown	Penicillin	2,000,000 units	8	Failure	Patient well 8 mo. after therapy
					Aureomycin	2-3 gm.	4	Failure	
					Chloromycetin	3 gm.	49	Probable cure	

*The antibiotics are listed according to the sequence of their administration.

†Penicillin, streptomycin and neomycin were administered intramuscularly; aureomycin and Chloromycetin were given orally except where otherwise indicated.

‡Patients were classified as cured when all evidence of endocarditis, such as positive blood cultures, fever and elevated sedimentation rate, were absent.

indicate that bacteriologic cure may be expected in the majority of cases. A review of 817 cases treated with penicillin during the past five years has revealed

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The aureomycin used in this study was supplied through the courtesy of Dr. Benjamin Carey, director of clinical research, Lederle Laboratories Division, American Cyanamid Company; the Chloromycetin by Dr. E. A. Sharp, director of clinical research, Parke, Davis and Company, Detroit, Michigan; and the neomycin by Dr. E. L. Burbidge, Upjohn Company, Kalamazoo, Michigan.

faecalis (enterococcus), being more resistant to penicillin, has been responsible for infections that have frequently posed problems of management and have yielded with great difficulty. In some instances, infections caused by penicillin-resistant *Str. faecalis* have responded to streptomycin or to the combination of streptomycin and penicillin.[4, 5] Streptomycin has been the agent of choice in the treatment of infections due to gram-negative bacilli.[4]

Although penicillin has completely altered the prognosis in subacute bacterial endocarditis, any

infection with a 30-percent mortality warrants further intensive investigation toward more effective methods of therapy. The introduction of aureomycin and Chloromycetin has raised the hope that these antibiotics may be effective against the organisms most commonly responsible for subacute bacterial endocarditis. Tests made in vitro have shown that these agents, in concentrations easily obtainable in the blood, inhibit the growth of both *Str. viridans* and *Str. faecalis* but, unlike penicillin, have little bactericidal effect.[6] In view of these considerations, a series of patients with subacute bacterial endocarditis were treated with aureomycin and Chloromycetin.

Table 2. *Minimal Concentrations of Various Antibiotics that Completely Inhibited the Growth of the Causative Organism in 10 Cases of Subacute Bacterial Endocarditis.*

Infecting Organism	Case No.	Minimal Inhibiting Concentration (after 48 hours)				
		Penicillin G	Streptomycin	Chloromycetin	Aureomycin†	Neomycin
		units	*microgm./ml.*	*microgm./ml.*	*microgm./ml.*	*microgm./ml.*
Str. faecalis	1	2.5*	1.67	6.25	2.5	—
	2	5.0*	2.5	10.0	0.625	3.12
	3	5.0	50.0	6.25	0.313	25.0
	4	0.005	5.0	2.5	0.079*	25.0
	5	0.079	2.5	5.0	0.158*	25.0
Str. viridans	6	0.019	2.5*	2.5*	0.313	25.0
	7	0.009	—	10.0	0.156	—
	8	0.039*	2.5	5.0	0.079	25.0
Staph. aureus	9	1.25	—	10.0	0.312	—
E. coli	10	—	3.13	25.0	3.13	0.9

*In-vitro sensitivity of the infecting organism against the antibiotic that effected the cure.
†Twenty-four-hour readings.

Clinical Material and Treatment

Eleven cases of subacute bacterial endocarditis were selected for study. The pertinent information concerning etiologic agent, antibiotic employed, dosage and duration of treatment, as well as the results, are summarized in Table 1. All patients except 1 (Case 6)* were hospitalized, studied and treated at the New England Center Hospital in Boston. The diagnosis was suggested by the presence of fever, cardiac murmurs, embolic phenomena, splenomegaly or anemia and was established by repeatedly positive blood cultures. Although repeated blood cultures were negative, 1 case (No. 11) is included in this series because the clinical picture was consistent with the diagnosis of subacute bacterial endocarditis. This patient manifested fever, anemia, splenomegaly and the murmurs of mitral stenosis.

The sensitivity in vitro of the infecting organism was determined against a number of antibiotics, including penicillin, streptomycin, Chloromycetin, aureomycin and neomycin. The results of the sensitivity studies are summarized in Table 2. The inhibiting levels of the various antibiotics in vitro as well as the blood levels when done were determined by the serial tube-dilution method described by Rammelkamp.[7] Streptococcus 98 served as the control organism in the determination of serum levels of aureomycin, Chloromycetin, penicillin and neomycin, whereas *Bacillus circulans* was used for streptomycin.

All cases were treated with aureomycin or Chloromycetin, either initially or after other antibiotics had failed to control the infection. The dose of the antibiotic administered depended on the sensitivity in vitro of the infecting organism. The average dose of aureomycin was 0.5 to 1.0 gm. orally every six hours. In 2 patients by whom the oral route could not be tolerated the drug was administered intravenously, as indicated in Table 1. The average dose of Chloromycetin was 1.0 gm. orally every six hours. In 3 cases, treatment with Chloromycetin was initiated with a priming dose of 1.0 gm. every hour for 4 doses. One case (No. 10) was treated with neomycin because of the failure of other antibiotics. The infecting organism in this case was *Escherichia coli* and studies in vitro suggested that this agent might be effective.

In all cases in which the blood level of the administered antibiotic was determined, adequate concentrations were obtained. The duration of therapy varied with each case, as is noted in Table 1. The cured cases were treated for five weeks, except as indicated.

Results

The results of therapy are summarized in Table 1. Eight patients were treated with aureomycin. In 4 cases this agent was used initially and in the remaining four only after other agents, usually penicillin, had failed. Because of the inaccuracies of the earlier methods for the determination of aureomycin blood levels, these were not done. The infection was considered to have been controlled in 2 cases (No. 4 and 5). Blood cultures became negative on the day after institution of therapy in Case 4. Aureomycin was given for seventeen days in this case but had to be discontinued because of nausea,

*This patient was hospitalized on the Third Medical Service (Tufts), Boston City Hospital.

vomiting and weight loss. At that time the sedimentation rate was normal and repeated blood cultures were negative. This patient then received penicillin therapy for seven days, but it seems highly unlikely that penicillin administered for such a brief period could be responsible for the favorable outcome. The blood cultures in Case 5 became negative on the day following institution of therapy. The progress of therapy in this patient is illustrated in Figure 1.

The infecting organisms in both cases were very sensitive strains of *Str. viridans*. Both these patients were followed for periods of eleven and twelve months respectively. Repeated blood cultures and the clinical course over this period of time

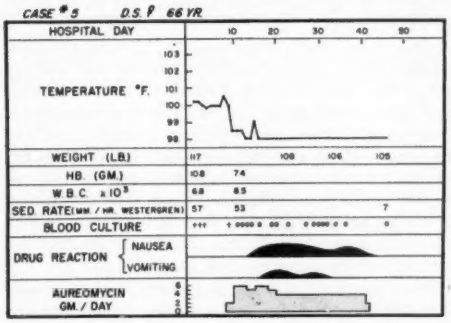

FIGURE 1. *A Case of Subacute Bacterial Endocarditis Successfully Treated with Aureomycin.*

indicated that there had been no relapse of the infection.

Aureomycin therapy failed in the remaining 6 cases (No. 1, 2, 3, 9, 10 and 11). Positive blood cultures could not be obtained in Case 11. In the remaining cases the blood cultures remained positive during the entire period of aureomycin therapy. The infecting organism in 3 cases (No. 1, 2 and 3) was *Str. faecalis*. Two of these cases (No. 1 and 2) were subsequently cured by large doses of penicillin. Case 2 was not cured on 8,000,000 units of penicillin daily but subsequently responded to the same dose of penicillin plus caronamide.

Chloromycetin was used in 5 cases (No. 6, 7, 8, 9 and 11). In only 1 case (No. 6) can it be said that a cure was definitely effected. The progress of therapy in this case is illustrated in Figure 2. Blood cultures became negative within twenty-four hours after institution of therapy. The total duration of therapy was thirty-five days. This patient was followed for five months after Chloromycetin was discontinued and there was no evidence of a relapse during that time. Two cases (No. 8 and 9) were definite failures on therapy. In Case 8, although the blood was sterile and the patient afebrile during the five weeks of therapy, relapse occurred two days after the drug was discontinued. This patient was finally cured by 2,000,000 units of penicillin daily for six weeks.

The infecting organism in Case 9 was *Staphylococcus aureus*. Six million units of penicillin daily, aureomycin and Chloromycetin all failed to cure the infection. Case 11, previously discussed in regard to aureomycin therapy, is included as a possible Chloromycetin cure after aureomycin had

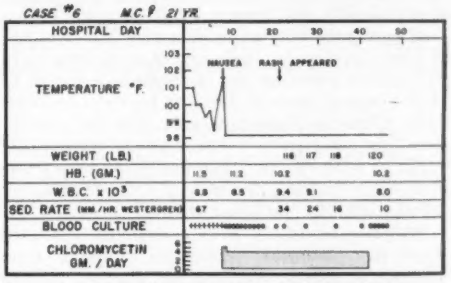

FIGURE 2. *A Case of Subacute Bacterial Endocarditis Successfully Treated with Chloromycetin.*

apparently failed. Despite many attempts, all blood cultures were sterile; hence the diagnosis of subacute bacterial endocarditis was not definitely established. The patient became afebrile and the sedimentation rate normal during Chloromycetin therapy, and there has been no relapse during the follow-up period of eight months.

Neomycin was used in 1 case (No. 10) because of the failure of other antibiotics and because the infecting organism (*E. coli*) was sensitive in vitro. Blood cultures became negative in twenty-four hours and remained so for the following five days, at the end of which time the patient died as a result of a cerebral embolus.

Discussion

The in-vitro sensitivity of most strains of *Str. viridans* and *Str. faecalis* to aureomycin and Chloromycetin has suggested that these agents may be effective in the treatment of subacute bacterial endocarditis. A review of the literature to date (Table 3) reveals that only 13 cases have been treated with aureomycin, of whom only 4 could be classified as cured.[6, 8-14] Most of the cases reported are part of a series of a variety of infections treated with aureomycin. As such, the sensitivity of the infecting organisms and the details of therapy are lacking in most reports. Only 2 reports have been published on the use of Chloromycetin in this infection.[12, 15] The etiologic agents in these cases were *Salmonella typhimurium*[15] and *Staph. aureus*.[12] Treatment with Chloromycetin in both cases failed.

In an endeavor to gather more information concerning the effectiveness of aureomycin and Chloro-

mycetin in subacute bacterial endocarditis, 11 patients were treated with these agents. Eight of the patients were treated with aureomycin. Only 2 could be classified as having been successfully treated (Cases 4 and 5). In both these cases aureomycin was used initially. In no instance was aureomycin successful when penicillin had previously failed. On the other hand, penicillin was successful in 2 cases (No. 1 and 2) in which aureomycin had proved ineffective. However, Dowling[12] reported a case of endocarditis successfully treated with aureomycin after penicillin had failed.

Of note is the failure of aureomycin in 3 cases due to *Str. faecalis*, an organism that is frequently resistant to penicillin and is responsible for 10 to 15 per cent of cases of subacute bacterial endocarditis. Cures in 2 cases infected with *Str. faecalis* have been reported.[10, 11] The hope that aureomycin might be more effective than penicillin in the treatment of endocarditis caused by *Str. faecalis* was not substantiated by our small series of cases.

All patients treated with aureomycin exhibited some gastrointestinal symptoms, varying from anorexia to nausea, vomiting and diarrhea. In one case (No. 4), the agent had to be discontinued after three weeks of therapy because of marked weight loss. Symptomatically, the patients do not seem to do so well on aureomycin as on penicillin. They usually lose weight and lack the sense of well-being generally noted shortly after the institution of penicillin therapy.

Of the 5 cases treated with Chloromycetin, only 1 could be definitely classified as a cure (Case 6). Another (Case 11) could not be so classified since no organisms could be cultured from the blood despite a classical clinical picture. It is of interest, however, to note that Chloromycetin produced a favorable clinical response after penicillin and aureomycin had failed.

Case 8 is of special interest. This patient received 4 gm. of Chloromycetin daily for two weeks followed by 3 gm. daily for three additional weeks. The blood cultures became sterile within twenty-four hours and remained so for the duration of therapy. The sedimentation rate during therapy returned to normal, but there was no gain in weight. Two days after Chloromycetin was discontinued the patient again became febrile and the blood cultures were positive. He was finally cured by 2,000,000 units of penicillin daily. Shortly after the onset of penicillin therapy the patient had a sense of well-being and gained 11 pounds in six weeks.

Whether relapse after the discontinuation of therapy such as occurred in Case 8 will be more frequent with aureomycin and Chloromycetin than with penicillin remains to be seen. Theoretically, since these agents, like the sulfonamides, are primarily bacteriostatic and have little bactericidal action, relapse may be more frequent than with an antibiotic like penicillin that exhibits both bacteriostatic and bactericidal properties.

It is of interest to note the one case (No. 10) treated with neomycin, since no reports have appeared on the use of this agent in subacute bacterial endocarditis. Neomycin was employed because Gantrisin, aureomycin, terramycin and streptomycin had failed and because tests in vitro indicated that the organism (*E. coli*) was sensitive to neomycin and resistant to Chloromycetin (Table 2). The blood cultures became negative and the patient afebrile twenty-four hours after neomycin therapy was instituted. However, she died on the sixth day of therapy as the result of a cerebral embolus. It is encouraging that negative blood cultures resulted shortly after therapy was instituted. If its neurotoxicity can be reduced this agent may be of value in similar cases.

Case 9 is worthy of comment. The causative organism was a hemolytic *Staph. aureus* and the patient was treated with penicillin, Chloromycetin and aureomycin alone and in various combinations. The blood cultures never became negative, and the patient died on the thirty-second day of therapy. It is of interest that post-mortem examination revealed virtually complete healing of the vegetations. A large splenic abscess was found from which *Staph. aureus* was cultured. It is possible that the positive blood cultures came from this source. The splenic abscess had been diagnosed prior to death, but splenectomy was not seriously considered because of the patient's poor physical condition.

It is of interest to compare the sensitivities in vitro of the infecting organisms against various antibiotics (Table 2). The organism (*Str. faecalis*) in Cases 2 and 3 was highly sensitive in vitro to aureomycin, yet this agent failed to effect a cure. Studies in vitro show that these same organisms were inhibited at levels of penicillin that could be obtained in vivo only by using very large amounts of this antibiotic. By the use of such amounts after smaller doses had failed, a cure was eventually effected in Cases 1 and 2. Twelve million units of penicillin daily were used in Case 1. In Case 2, 8,000,000 units daily failed, but when this same amount was combined with caronamide the outcome was successful. Penicillin failed to control the infection in Case 3, probably because of inadequate dosage.

The 2 cases cured by aureomycin (Cases 4 and 5) were caused by aureomycin-sensitive strains of *Str. viridans*. Aureomycin failed in Case 9 despite the fact that the organism (*Staph. aureus*) was sensitive in vitro.

Chloromycetin was successful in Case 6, in which the infecting organism (*Str. viridans*) was only moderately sensitive. Case 8 was infected with a moderately resistant organism and Case 9 with a highly resistant one; in both these patients Chloromycetin failed to control the infection.

In general, Chloromycetin was more readily tolerated than aureomycin. Only 1 patient (No. 6) complained of nausea, and this occurred during the initial priming dose. Two patients developed a mild maculopapular rash over the face and neck. Although sore tongue, diarrhea and pruritus have been reported, these were not manifested in this study.

Although the determination of the sensitivity in vitro of the causative organism remains the best guide to the choice of the most effective antibiotic, it is apparent that a sensitive organism will not necessarily respond to the antibiotic that appears to have the greatest effectiveness in vitro. For this reason it is essential to make sensitivity studies against all available antibiotics in order to be able to choose a substitute without delay when it becomes apparent that the antibiotic currently employed is ineffective.

The sensitivities in vitro of the infecting organisms are listed in Table 2. In general, except for toxic effects resulted from such high doses. In contrast, with aureomycin and Chloromycetin few patients are able to tolerate a maximum dose of 6 gm. daily, which represents only a twofold increase in the average dose of 2 to 3 gm. The elasticity of penicillin dosage should be taken into consideration in interpreting the inhibiting levels of the various antibiotics employed in vitro. Also to be considered is the enhancement of blood levels that can be obtained with such agents as caronamide and benemid, making the same penicillin dosage even more effective. This is illustrated in Case 2, in which 8,000,000 units of penicillin alone failed, whereas 8,000,000 units of penicillin plus caronamide was successful.

Conclusions

Aureomycin and Chloromycetin may effect a bacteriologic cure in certain cases of subacute bacterial endocarditis due to sensitive organisms.

Table 3. *Aureomycin and Chloromycetin Therapy of Subacute Bacterial Endocarditis. Results in 14 Previously Recorded Cases.*

Author	No. of Cases	Infecting Organism	Antibiotic	Results
Allen and Riecker	1	Hemolytic *Staph. aureus*	Aureomycin	Apparent cure
Hunter[6]	1	*Str. liquifaciens* (enterococcus)	Aureomycin	Failure
Brainerd et al.[9]	2	*Str. faecalis* (enterococcus)	Aureomycin	Failure
Harvey et al.[10]	2	*Str. faecalis*	Aureomycin	One failure; second patient well after 5 months
	2	Microaerophilic streptococcus	Aureomycin	Failure
Schoenbach[11]	1	*Str. salivarius*	Aureomycin	Failure
	1	*Str. faecalis*	Aureomycin	Patient well after 7 months
Astler and Morgan[13]	1	*Staph. aureus*	Aureomycin Chloromycetin Terramycin	Failure on all 3 antibiotics
Dowling et al.[12]	1	Mixed *Staph. aureus* and alpha- and beta-hemolytic streptococcus	Aureomycin	Apparent cure
Pillsbury and Fiese[14]	1	Nonhemolytic enterococcus	Aureomycin	Failure
de Swiet[15]	1	*S. typhimurium*	Chloromycetin	Failure

Str. viridans, the organisms were more sensitive to aureomycin that to the other antibiotics. In all instances, *Str. viridans* was most sensitive to penicillin. However, other factors than the comparative inhibitory levels of the various antibiotics in vitro should be considered in choosing the most effective antibiotic in the treatment of subacute bacterial endocarditis. Higher blood levels can be obtained with Chloromycetin than with aureomycin. Another factor to be considered in the choice of the most effective antibiotic is its elasticity of dosage. By this is meant the range between the average dose and the maximum dose that can be employed. The average dose of penicillin currently employed in the treatment of subacute bacterial endocarditis is 800,000 to 1,000,000 units daily. In this study it was necessary to administer 12,000,000 units daily before cure could be effected. This represents a twelvefold increase in dosage. No

An organism found to be sensitive to aureomycin and Chloromycetin in vitro will not necessarily respond in vivo.

In this small series aureomycin and Chloromycetin were not successful when penicillin had previously failed. On the other hand, penicillin was successful when these antibiotics did not control the infection.

Patients seem to do better symptomatically on penicillin therapy.

Although further studies are necessary before definite conclusions can be drawn, these studies indicate that penicillin is the antibiotic of choice in the therapy of subacute bacterial endocarditis due to *Streptococcus viridans* and *Streptococcus faecalis*. If large doses of penicillin or the combination of penicillin and streptomycin prove ineffective, aureomycin or Chloromycetin should be tried if in-vitro studies are favorable.

We are indebted to Miss Joan Jackler and Mrs. Elizabeth Lyons for their valuable technical assistance and to the House Staff of the New England Center Hospital and the First and Third Medical Services of the Boston City Hospital.

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A COMPARATIVE STUDY OF PREGNENOLONE, 21-ACETOXYPREGNENOLONE AND ACTH*

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BOSTON

THE evaluation of new drugs in the treatment of rheumatoid arthritis and spondylitis has become a grave responsibility of the medical profession. Since the scarcity of ACTH and cortisone, as well as their limitations and side-effects, is now generally known, favorable recommendations of new drugs based on clinical experience are likely to cause unrest and new hopes among those suffering from disabling rheumatic disease.

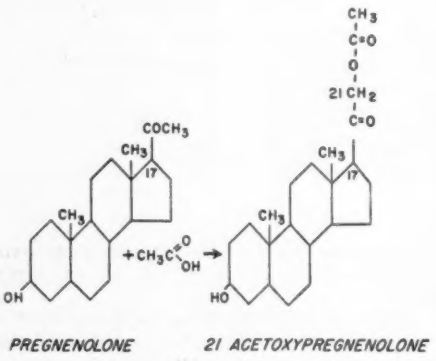

FIGURE 1.

Certain drugs that have been the object of recent clinical studies and subsequent publicity are steroids of the pregnenolone, pregnenolone acetate, 21-acetoxypregnenolone and pregnenolone diacetate group (also known by various brand names such as prenone, artisone and so forth).

The chemical properties of pregnenolone have been reviewed recently by Henderson, Weinberg and Wright.[1] The structure of pregnenolone and 21-acetoxypregnenolone is shown in Figure 1.

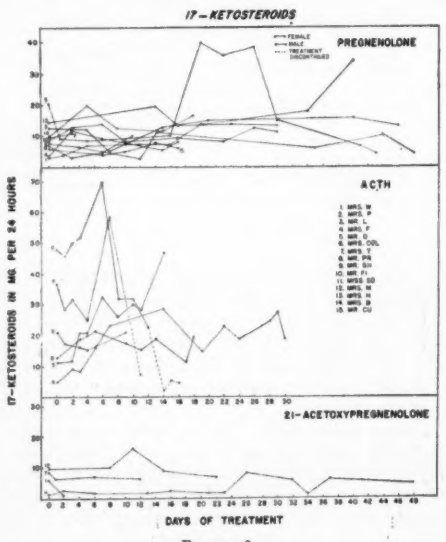

FIGURE 2.

The relation of these drugs to progesterone is close; actually, pregnenolone is obtained in the last

*This study was aided by a grant from the Schering Corporation, Bloomfield, New Jersey. The chemical analyses were performed by Mr. John Papilios.

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stage of the synthesis of progesterone. Its preparation from cholesterol is easily accomplished. This is borne out by the observation that in our patients pregnenolone administration was followed by the appearance of small quantities of pregnanediol in the urine and a decrease of the 17-ketosteroids (with the exception of one case of spondylitis in which the ketosteroid excretion remained high). Its lack of toxicity has been verified in numerous experimental and clinical trials. We have given as much as 1200 mg. daily without any side-effects other than hard, painful lumps at the site of injection.

The possible usefulness of these drugs was first suggested by Lansbury in 1946 (cited by Henderson) and further brought out by Ishmael and his coworkers in Oklahoma.[2] These authors used pregnenolone alone and found improvement in some patients. If pregnenolone was given in combination with testosterone

TABLE 1. *Case 2.*

DATE	DRUG	DOSE	17-KETOSTEROIDS	BLOOD EOSINOPHILS	BLOOD SEDIMENTATION RATE	WEIGHT	DEGREE OF DISABILITY	REMARKS
		mg.	*mg./24 hr.*	*no./cu. mm.*	*no./1 hr.*	*lb.*		
9/15/49	Pregnenolone	0			70	147	+++	
9/22/49	Pregnenolone	100				144	++	
9/29/49	Pregnenolone	200				146	++	
10/ 6/49	Pregnenolone	300			39	146	+	
10/13/49	Pregnenolone	300			26	146	+	
10/20/49	Pregnenolone	300				146	+	
1/23/50	ACTH	80	9.8	90	33	141½	+++	
1/24/50	ACTH	80		24			++	
1/25/50	ACTH	80		27			+	
1/26/50	ACTH	80	11.0	17	39		+	
1/28/50	ACTH	80			33	141	+	
1/30/50	ACTH	80		25				
1/31/50	ACTH	80	37.0	16	16	150	+	
2/1/50	ACTH	40	23.8	5			+	
2/2/50	ACTH	40	31.5	0			0	
2/3/50	ACTH	40			3	152	+	Edema
2/4/50	ACTH	20	25.0	7			+	
2/6/50	ACTH	20		11			++	
2/7/50	ACTH	20	58.4	9			++	Edema subsided
2/8/50	ACTH	20		31				
2/9/50	ACTH	20		19			++	
2/16/50		0	7.5	159		137	+++	
4/13/50	Acetoxypregnenolone	300	8	87	30	151	+++	
4/15/50	Acetoxypregnenolone	300	6.4	93			++	
4/26/50	Acetoxypregnenolone	300	7.0	206	35	155	++	
5/4/50	Acetoxypregnenolone	300	6.4	187	36	156	++	
5/11/50	Acetoxypregnenolone	300		281	42	161	+	Edema

TABLE 2. *Clinical Results in 20 Patients Treated with Pregnenolone, 21-Acetoxypregnenolone or ACTH.*

CASE NO.	AGE	SEX	GRADE	DURATION OF ILLNESS	PREGNENOLONE					ACETOXYPREGNENOLONE					ACTH	
					TOTAL DOSAGE	DURATION OF TREATMENT	BLOOD SEDIMENTATION RATE	WEIGHT GAIN OR LOSS	IMPROVEMENT	TOTAL DOSAGE	DURATION OF TREATMENT	BLOOD SEDIMENTATION RATE	WEIGHT GAIN LOSS	IMPROVEMENT	TOTAL DOSAGE	IMPROVEMENT
				yr.		*days*	*mm./hr.*	*lb.*	*%*	*mg.*	*days*	*mm./hr.*	*lb.*	*%*	*mg.*	*%*
1	34	F	3	20	7,900	50	†71–96‡	0	10						900	75
2	47	F	2	5	5,500	28	65–39	0	50	21,000	21	30†–42‡	+6	75	780	100
3	58	F	4	3	3,700	15	88–95	0	0						750	50
4	38	F	3	18	13,000	21	58–58	0	25						450	90
5	60	F	3	25						5,400	19	59–65	−1	0	300	100
6	37	F	4	5						9,000	30	50–25	+2	0	445	50
7	46	M	3	3						2,100	7		+1	0	600	75
8	42	M	3	30	4,000	21			0						426	75
9	20	M	4	4						2,100	7	20–20				
10*	58	M	3	2	9,350	60	28–45	0	0							
11	44	F	3	20	17,900	52	14–25	0	20							
12	28	F	2	½	4,150	21	6–25	+1	0							
13	67	M	3	17	6,000	28	58–50	0	0							
14	51	F	2	½	900	8	26–?	?	0							
15	64	M	2	20	4,000	16	70–56	−5	0							
16	79	M	3	30	4,200	21	not done		0							
17	32	F	3	15	8,700	42	55–54	0	0							
18	40	F	2	2	1,400	8	50–41	?	0							
19	51	F	2	2	5,400	28	55–50	−4	0							
20	53	F	3	5	7,000	28	55–50	−2	10							
21	45	M	2	5						5,100	17	36–46	−3	0	600	100

*Gout.
†Before treatment.
‡After treatment.

improvement was observed in 65 per cent within twenty-four hours. Less enthusiastic but still promising reports were published by Davison, Koets and co-workers[3] and by Freeman and Pincus from the Worcester Memorial Hospital.[4] The last mentioned authors employed pregnenolone orally in doses of from 100 to 700 mg. and treated 30

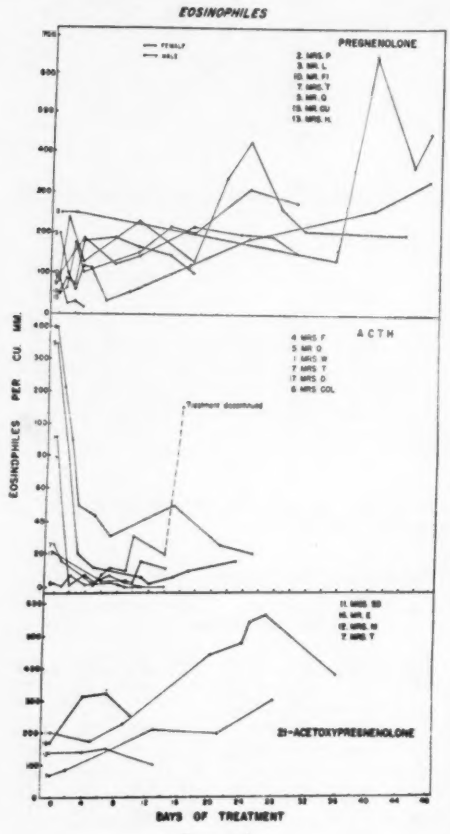

FIGURE 3.

patients for at least six weeks. They reported "striking relief" in 15 patients, mild improvement in 11 and 4 failures. Guest and his co-workers,[5] however, treated 19 patients suffering from chronic rheumatoid arthritis with pregnenolone in doses of 100 to 300 gm. "daily in the majority of the cases, but a few patients received injections only two or three times a week." They found no improvement in 17 cases. One patient with rheumatoid spondylitis improved objectively and subjectively; one showed mild transitory improvement.

In addition to pregnenolone, various pregnenolone derivatives such as 29-monacetic and diacetic pregnenolone were studied because of experimental evidence that suggested that these drugs affected the permeability of joint membranes. Dyes, such as phenolphthalein, injected into the ankle joints of rabbits, were excreted more slowly when certain pregnenolone derivatives were given. An antihyaluronidase effect was therefore assumed. The only clinical report available is contained in an oral report by Fitch, Warter and Seifter[6] on 17 patients, 15 of whom showed "marked improvement."

Administration. Pregnenolone* was given to 16 patients in daily intramuscular injections of an oily suspension (later an aqueous suspension) in doses ranging from 100 to 600 mg. Two patients received 2 daily injections up to a total of 1200 mg. per day. The injections were continued for four to eight weeks.

21-acetoxypregnenolone was given to 6 patients in daily intramuscular injections of an aqueous suspension in doses from 100 to 300 mg. for two to four weeks. Two patients requested discontinuation of the drug because of discomfort at the site of injection.

ACTH was given to 9 of these patients (in the form of a preparation made according to the method of Payne, Raben and Astwood.[7, 8] This preparation, obtained from dried pituitary glands by extraction with glacial acetic acid, has proved twice as active as the Armour Standard LA-1-A. We obtained maximal effects in most of our patients with 15 mg. given subcutaneously every eight hours. Optimal improvement was achieved within a few days and maintained for the purpose of this study over a period of two to three weeks.

Experimental Results

Twenty-one persons were studied. Sixteen patients were treated with pregnenolone, 6 with 21-acetoxypregnenolone; an additional course of ACTH was given to 9 patients. Eighteen patients suffered from severe chronic rheumatoid arthritis (one accompanied by psoriasis), 2 from ankylosing spondylitis and 1 from polyarticular gout. All patients were partially disabled and one was actually bedridden. They fell into Grades 2 and 3 of the classification suggested by Steinbrocker. All showed definite rheumatic activity as indicated by pain, joint swelling, malaise and blood changes (mild anemia, elevation of sedimentation rate). Three patients showed frank marasmus. In two, typical rheumatic nodules were present, both exhibiting marked rheumatic activity on removal.

In most patients treated with pregnenolone there was some decrease of discomfort for short periods of time. This was similar to the effect of large doses of salicylates and did not represent a sustained

*Pregnenolone and 21-acetoxypregnenolone were supplied through the courtesy of Dr. Henderson of the Schering Corporation.

action of the drugs. One patient observed temporary relief from pain lasting throughout the course, but some stiffness remained; the patient's well-being could not compare with the freedom of motion that she experienced during ACTH therapy. Only one patient felt considerably better at the end of treatment, which in her case was carried out over a period of two months.

This patient (Table 1) was improved to a still greater degree with ACTH. After ACTH therapy was discontinued she suffered a marked withdrawal relapse and was then given 21-acetoxypregnenolone in daily doses of 300 mg. She improved again. After three weeks she developed extensive edema of the legs and a weight increase of 6 pounds within 7 days that could not be explained by any obvious imbalance of the electrolytes or cardiovascular disease. The whole course suggests to us the possibility of a spontaneous remission.

Figures 2 to 4 show the effects of pregnenolone and 21-acetoxypregnenolone upon blood eosinophils, blood sedimentation and 17-ketosteroids. The 17-ketosteroids were found to be depressed in all but one case, whereas the number of circulating eosinophils was elevated in all cases after a short decrease. The eosinophilia coincided in two patients with a mild skin rash. In contrast, after administration of ACTH we observed rapid decrease of the eosinophils and sedimentation rate as well as marked increase in 17-ketosteroids, findings now recognized as evidence of adrenal cortical activity.

A summary of all the cases treated is given in Table 2. It shows that with the exception of the one patient mentioned, the injection of pregnenolone and 21-acetoxypregnenolone did not produce any noticeable improvement of joint function, gain of weight or return of the sedimentation rate to normal or even noticeably lower values. The various blood constituents examined, such as hemoglobin and white blood cells, also remained unchanged. Rheumatic nodules did not disappear or change in 2 patients, although one patient showed decrease in

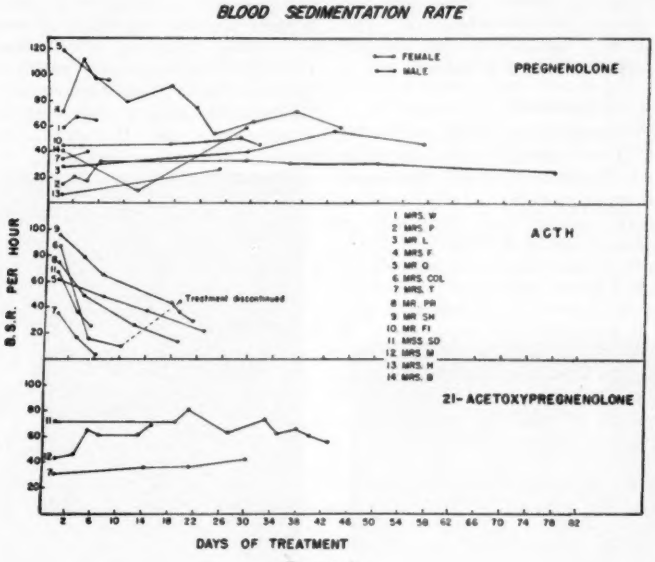

FIGURE 4.

TABLE 3. *Side-Effects Observed in the Use of Pregnenolone, 21-Acetoxypregnenolone and ACTH.*

DRUG	LOCAL	GENERAL
Pregnenolone (16 patients)	Hard, lumpy deposits One local abscess	Urticaria (2 patients) Anxiety (1 patient) Prolonged menstrual periods (2 patients)
Acetoxypregnenolone (5 patients)	Hard, lumpy deposits	
ACTH (9 patients)	Local redness and itching (on withdrawal)	Personality changes Rapid weight gain Angioneurotic edema (1 patient, on withdrawal)

number and size of nodes under treatment with pregnenolone.

The last column of Table 2 shows the rapid clinical recovery during the course of ACTH in all 9 patients previously treated with pregnenolone or 21-acetoxypregnenolone.

Side-effects were rare and usually due to painful sensations at the site of injections. Repeated injections caused formation of firm lumps that persisted in some patients for several months. Prolonged menstrual flow occurred in two patients. The side-effects are summarized in Table 3.

Discussion

It is difficult to reconcile our results with those found by some of the authors mentioned earlier and others cited in Henderson's review. One reason for our poor results is probably the rigid selection of patients, which included only those suffering from chronic active rheumatoid arthritis. Furthermore, we felt strongly that such terms as "striking" or "marked" could not be applied to changes that occurred during the course of treatment with pregnenolone or 21-acetoxypregnenolone, with the exception of one case reported in detail.

The foregoing study gives occasion to point out once more the difficulty that is encountered in the appraisal of new drugs. Since the medical profession will soon have available ACTH or cortisone, it seems worth while to use these drugs in short courses to "titrate," so to speak, new antirheumatic remedies against the maximal therapeutic effect obtainable. The search for a lastingly effective and also innocuous drug for the treatment of severe active rheumatoid arthritis is still in progress. Pregnenolone and 21-acetoxypregnenolone do not, in our opinion, represent such a drug.

Summary

Twenty patients suffering from rheumatoid arthritis and 1 patient with gout were treated. Fifteen received injections of pregnenolone and 6 received injections of 21-acetoxypregnenolone in various amounts over periods from seven to forty-two days. Nine of these patients were treated subsequently with a course of ACTH. Neither pregnenolone nor 21-acetoxypregnenolone could produce a sustained beneficial effect comparable to the effect obtained with ACTH.

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MULTIPLE HYPERNEPHROMAS OF THE KIDNEY IN ASSOCIATION WITH LINDAU'S DISEASE

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IN 1911, von Hippel[1] described the condition of angiomatosis of the retina. After making a study of cerebellar cysts, Lindau[2] subsequently pointed out that 20 per cent of patients with angiomatosis of the retina have intracranial complications consisting of cerebellar cysts or angioblastic tumors in the cerebellum and medulla oblongata. In addition to these intracranial complications, Lindau described the not infrequent occurrence of cysts of the pancreas and cysts or hypernephroma of the kidney. He pointed out that although the intracranial lesion may be angiomatous the abdominal lesions are not vascular; he considered the tumors of the kidney to be of benign, hypernephroid type. The renal lesions are not necessarily benign, as was shown in the case reported by Kernohan,[3] in which multiple carcinoma of the kidney with metastasis to the omentum was described.

The following case of multiple hypernephromas of the right kidney in association with angiomas of the retinas and hemangioendothelioma of the cerebellum is reported because of the infrequent occurrence of the syndrome.

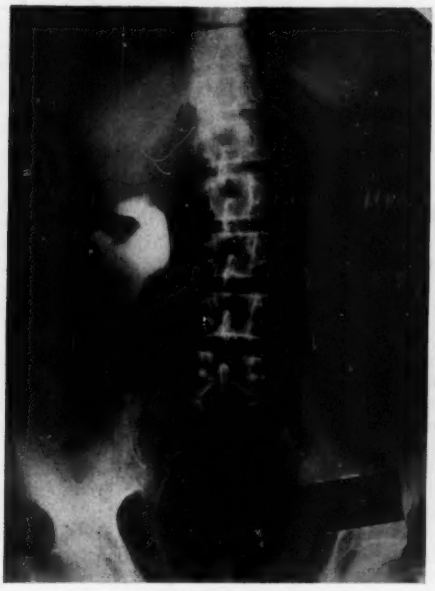

FIGURE 1. *Right Retrograde Pyelogram.*
There is evidence of enlargement of the renal outline and pelvis and of blunting of the calices, with a filling defect of the middle and lower calices.

CASE REPORT

A 62-year-old woman presented herself for examination in December, 1938, because of nausea, vomiting and constipation of seven months' duration. These symptoms occurred in attacks approximately once weekly. Concomitantly she had noted morning headaches, inability to read well, constant vertigo and inco-ordination of her lower extremities.

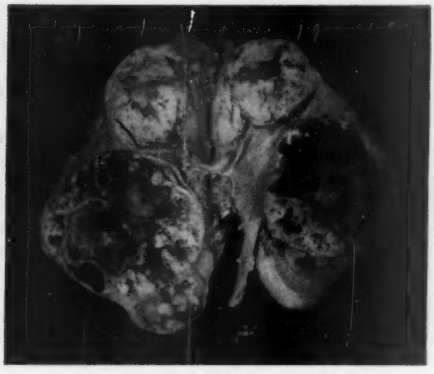

FIGURE 2. *Photograph of the Excised, Opened Kidney.*
A large hypernephroma occupies the lower pole and a second, smaller hypernephroma, the upper pole.

Pertinent physical findings were obtained by neurologic examination. A typical angioma was seen in the upper temporal quadrant of each ocular fundus. Cerebellar ataxia was noted. Routine laboratory studies gave normal or negative results, except that mild pyuria was evident and *Escherichia coli* were found in the urine. A plain roentgenogram of the urinary tract was reported to be negative.

A diagnosis of Lindau's disease was made and was followed by cerebellar craniotomy. A cyst containing a mural nodule was removed from the superior lateral portion of the left cerebellar lobe. After microscopical study of the excised cyst a diagnosis of hemangioendothelioma was made.

Convalescence was uneventful. Striking improvement in symptoms and objective findings were readily apparent and the patient was dismissed from our care.

She returned in August, 1946, because of constipation and insomnia of three months' duration. She had experienced

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no urinary symptoms. The previous neurologic symptoms had disappeared. A freely movable, hard, irregular mass was felt in the right upper quadrant of the abdomen; this was interpreted as an enlarged right kidney. The ocular fundi were unchanged.

Routine blood counts yielded normal results. Roentgenographic examination of the thorax and colon were negative. The concentration of urea was 30 mg. per 100 cc. of blood. Urinalysis disclosed mild pyuria, and the presence of micrococci was detected by culture.

The urinary tract was studied by excretory urography, cystoscopy and retrograde pyelography. The lower pole of the right kidney appeared enlarged and the pelvis and calices moderately dilated; the lower calix was deformed by a filling defect (Fig. 1). The left kidney appeared normal.

In view of the previous diagnosis of Lindau's disease, a presumptive diagnosis of cyst or hypernephroma of the right kidney was made, and surgical exploration was carried out. The gross appearance of the kidney suggested hypernephroma, and nephrectomy was performed. The kidney weighed 390 gm. On section of the kidney a hypernephroma, 7.5 by 8 cm., was found in the lower pole and a similar but smaller mass, 4 by 4.5 cm., revealed in the upper pole (Fig. 2). Sections were removed from each mass and microscopical study corroborated the diagnosis of hypernephroma. Convalescence was uneventful and the patient was dismissed from our care and returned to her home in California.

In 1948, two years after the patient's dismissal, we suggested that she undergo urologic study. We are indebted to Dr. Elmer Belt, of Los Angeles, who carried out the investigation. He reported that the patient was asymptomatic and that the solitary left kidney was normal on pyelographic examination.

In response to an inquiry we learned that the patient was well just before this report was written, late in 1950. This was twelve years after the diagnosis of Lindau's disease had been made.

Summary

A case report describing the occurrence of two distinct hypernephromas of the right kidney in association with Lindau's disease is presented.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SOCIAL INSTRUMENT: INDUSTRIAL MEDICINE

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FROM inconspicuous beginnings as a minor offshoot of general medical practice, industrial medicine has developed in the last half-century into a humane science concerned with all the facets of man's physical, mental and emotional actions and reactions at work. Its growth paralleled the rise of our nation to world supremacy as an industrial and economic power. As our society changed and became more complex over the years and as the industrial population increased to vast numbers, concentrated in ever larger groupings or scattered in diverse segments, the need for far-reaching industrial health programs was intensified.

During the first two decades of the century, the range of industrial medicine was narrow and limited to the care of trauma and specific occupational diseases. The experiences of World War I, highlighting the injurious effects of certain toxic substances that suddenly came into wide industrial usage, stimulated a new and fruitful interest in control of the physical environment of the plant. It was not until the second world war, however, that industrial medicine took its place as a significant force in the life of the nation. The introduction of dynamic procedures for improving the workers' health became imperative. Tremendous production requirements, combined with the drawing off of large elements of the working population for war service, forced industry to conserve and make the utmost use of the remaining manpower. Industrial medicine was challenged as never before to maintain the optimum physical condition of workers, including the handicapped or over-age, who formerly would have been discarded as unfit.

In pursuit of the goal of industrial health, it was found that the employee's occupational situation was a dominant factor in his total well-being. Health on the job was reflected in — and affected by — the environment at home and in the community. This realization led farsighted managements and doctors to investigate the whole field of worker welfare, and the base of the practice of industrial medicine is becoming so broad as to establish industrial medicine a social science in its own right.

Interdependence of Medicine and Industry

The interdependence of medicine and industry is a striking feature of the over-all picture at this mid-century. Industry would have foundered and the industrialization of our society would have been checked without the medical advances of the last fifty years, particularly those in the field of public health. Control of epidemic diseases and provision

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of safe water supply and safe sewage disposal were prerequisites for those living in the close proximity essential to modern industrial production methods. That the lack of such public-health control can result in industrial backwardness is evident in various parts of the world, especially in large areas of India and Africa, where the grip of malaria and other epidemic diseases prevents large-scale urbanization to this day.

At the beginning of the century, industry turned slowly and on the whole reluctantly to the medical sciences for help. There were ignorance and indifference toward occupational disease on the part of both manufacturers and physicians. This was the period of an abundant, never failing supply of cheap manpower, made up largely of immigrants from Europe, who accepted exhausting and dangerous work as inevitable. Their attitude was unquestioned, even encouraged, by many industrial managements. However, with the pioneering investigations of physicians in the second decade, enlightenment spread in the industrial world and employers began to welcome new technics for raising their workers' health standard. The movement gained momentum with each new legislative reform during the years around 1910, when the individual states and then the Federal government enacted a series of laws securing the rights of labor and regulating industrial practices. Nevertheless, manufacturers had recourse to medical collaboration only here and there and in only a certain few industries.

Not until World War I did the dependence on medicine for further industrial progress become apparent. Almost overnight, toxic substances — notably, radium, TNT and benzene — were put to industrial use on a widespread basis and in larger quantities than ever before, threatening hazardous exposure to greatly increased numbers of workers. The urgency of the situation dictated the swift expansion of industrial medicine, in contrast to its slow accretion of knowledge concerning occupational diseases during the preceding decades. Industry's reliance on medical research and practice steadily grew after the first world war, although not at the accelerated pace of the war days.

A second, more powerful impetus, with more momentous consequences for both industry and medicine, was provided by World War II. The unprecedented demands made on our country in its new role as industrial arsenal of the world could be met only with the close co-operation of industrial medicine. Most dramatic of the many evidences of industry's need for medical guidance was that in the field of atomic energy. Whether as a war project or for use in peacetime, the industrial development of atomic radiation is dependent on the efficacy of modern industrial medical practice. So vital is the factor of health protection for industrial personnel, as well as for the public at large, that atomic-radiation installations today allot 5 per cent of their total expenditures directly to health measures. It has been estimated that 75 per cent or more of the total construction and operating costs in the development of atomic energy have been dictated by health considerations. Further progress in the production and use of atomic energy will be subject to the effectiveness of protective measures and the broadening of knowledge concerning radiation in relation to human physiology.

In the same way, the future of beryllium depends on the progress of medical science. Noteworthy for the last two decades, beryllium became indispensable during World War II, not only in the building of the atomic pile, but in the manufacture of many metallurgic products. Certain compounds of beryllium have been shown to produce a delayed, chronic, fatal type of disease, but all the factors are still not known. Undoubtedly beryllium will continue to be used, since it has such qualities that modern industry cannot afford to relegate it to the status of a laboratory curiosity. Literally scores of papers have been published on beryllium poisoning in the past ten years, despite the fact that only a small number of workers have been affected. This intense interest has grown out of the need to arrive at a sound understanding of the clinical effects, as the first step in the development of protective measures.

An example of the many other challenging avenues of medical research that are constantly being opened today at industry's instigation is that of "space medicine." The former characterization, "aviation medicine," is no longer appropriate to define that branch of medical science responsible for solving problems involving rarefied atmospheres, gravitation, centripetal and centrifugal forces and cosmic rays. Man's mastery of space will depend on the ability of medicine to match present and future developments in the aviation industry.

Although it is obvious that over the past half-century industry has leaned more and more on medicine, it cannot be denied that industry in turn has had a substantial influence on medicine — not alone on that phase of medicine applied to the industrial situation but on medical practice in its entirety. Our nation's living and health standards during these fifty years have been the direct outcome of our economic strength. At the end of the last century our productive industrial economy had already laid the foundation for a health standard unsurpassed elsewhere in the world. During the decades that followed, our medical standards were upheld and raised to progressively higher levels as a result of our widely distributed and productive economy. Technical medical innovations obviously contributed to the general upward trend, but the decisive factor in medical progress responsible for our lessened morbidity and increased longevity was our superior industrial social system. As an illustration, the mortality and morbidity rate from

tuberculosis in a given community depends largely on the local economic situation, reflected in the degree of congestion, the adequacy of housing, nutrition and clothing and the general level of education. These contingencies, as well as the availability of medical care, are acutely affected by the community's economic status.

Through development of the technical sciences, industry has supplied another, more immediately discernible re-enforcement to medicine in the last half-century, particularly in the last twenty years. The laboratory, diagnostic and therapeutic equipment used in medical practice today and the extensive distribution of drugs are made possible only through industry's ingenuity. As in other phases of industrial and medical progress, technologic growth was gradual in the beginning of the century, spurted ahead during World War I and made startling advances during and after the second world war.

Development of Preventive Industrial Medicine

From the interlocking interests of industry and medicine at this half-century has emerged the new concept of industrial medicine as a social science. At the turn of the century it would have been foolhardy to predict that industrial medicine would advance along the fluid front it now occupies. Equally unforeseeable was its transformation into a field of public-health and preventive medicine. Industrial medical practice in the early 1900's existed only as a localized activity dealing with the treatment of occupational injuries and illnesses. America lagged far behind Europe, where the industrial revolution had long pointed up the health problems of workers. In the western European countries there were many physicians who devoted themselves to the care of occupational injuries and illnesses and to the medical regulation of the factories and workmen's compensation laws.

Here, however, the movement did not get under way until the end of the first decade, when passage of workmen's-compensation acts in our major industrial states resulted in the provision of medical services for the industrially injured. The employer's obligation to defray costs arising from a worker's injury necessitated prompt first aid, early return of function, minimal cost and accurate evaluation of disability. As a result, there came into being specialists in the field of industrial trauma who were cognizant of these extraneous factors. Disability evaluation and handling of workmen's-compensation cases became a special art. Although there are unmistakable signs that the main function of industrial medicine in the future will be preventive in nature, the occupational physician's fundamental duty at the present time remains the care of trauma suffered at work.

The employers'-liability laws and the rapid industrialization of our economy created other problems that could be solved only by the introduction of preventive medicine in the industrial framework. The first aspect of preventive industrial medicine to be developed was accident prevention. Under the workmen's-compensation regulations, accidents and later illnesses due to hazardous working conditions came under the heading of added production costs. Industrial managements, in order to keep abreast or ahead of their competitors, became seriously interested in safety. Until about 1920, accident prevention consisted essentially of engineering revision and plant inspection, but in the 1920's the concept of participation of the individual workers in accident-prevention programs was developed. Safety engineers acquired new roles as educators, in addition to their former ones, and the training programs then instituted to promote safety-mindedness among employees continue in effect today. The combined attack on unsafe environmental conditions and unsafe practices produced generally excellent results, all the more creditable in view of the fact that potentially hazardous materials and processes were continually being introduced. The nationwide industrial-accident frequency dropped steadily over the years until about 1932, but since then the frequency curve, although not rising to any appreciable degree, has not moved significantly downward.

Interest in the personal factor to which could be traced a great majority of industrial accidents gradually grew during the period from 1930 to 1940. Industrial physicians who had been conducting preemployment physical examinations since about 1910 began to use new and more effective technics for evaluation of the individual worker and to guide management in selective placement. Through medical investigation came awareness of the close relation of the worker's emotional health to his physical health and general mental and physical effectiveness as well as to his accident record. The last decade of industrial medical practice has brought the psychiatric aspect of workers' health to the forefront, so that at this mid-century the psychodynamic make-up of the individual worker is of equal interest with his physical and physiologic characteristics.

Various technics to ameliorate or correct emotional instability in employees are now in use, and the continuing study of this aspect of industrial medical practice holds great promise for the future. In arriving at an understanding of the individual's psychodynamic composition, interviews by the medical director, testing procedures using projective technics and, if needed, referral for psychiatric study to a competent specialist are undertaken. The comparatively recent interest in the psychiatric aspects of worker health does not imply any lessening of interest in environmental control.

On the contrary, present-day industrial hygienists and safety engineers are more alert than ever to the need for vigilance against harmful vibration, noise, monotony, crowding, neglect of plant housekeeping or machine guarding and the dangers of processes involving toxins. The physician, too, maintains a close watch over the constantly changing physical conditions of the industrial scene. His familiarity with the working environment is essential if he is to fulfill what is now considered one of his most important functions, namely, assistance in the selective placement of employees.

Selective placement is one of the notable gains of recent years and reflects the reorientation of management's and labor's attitude toward industrial health. The pre-employment physical examination, which is of course one of the essential concomitants of proper job placement, was not always viewed in its present light. At its inception the physical examination before employment was merely a screening process for eliminating bad compensation risks, without regard for the applicant's capacity to do the work for which he was applying. Hence, when first adopted it merely served to carry out the laws governing workmen's compensation. Moreover, the worker's chance of replacement in a job suited to his altered capacity after injury was dubious under the schedules in the laws that relieved the employer of the obligation of re-employment on the payment of a fixed amount of money. Revisions were called for, and industrial medicine through the years concerned itself more and more with complete rehabilitation and appropriate replacement of the disabled worker. In the past two decades, stimulated especially by the limited manpower available during World War II, technics were developed of matching the worker's physical capacities with the demands of the job. Experience has proved that individuals so placed are industry's strongest defenses against costly occupational disability. Industry has gone farther and found that it pays not only to place the worker selectively and to prevent his illness but to keep him in optimum physical condition.

It is noteworthy that the pre-employment examination was resented by labor, which charged that it was misused as a pretext for discriminatory employment practices. The policy of conducting examinations brought industrial medical departments into disrepute. Labor-management relations actually were damaged rather than bettered by many industrial medical programs. That there have been abuses of the pre-employment examination cannot be denied, but in the past decade a number of factors have intervened to change the attitudes of all concerned. The experiences of World War II, the spread of seniority rules and union shops, the general industrial stabilization of our population and the greatly augmented employment of older workers have forced the change. Today physicians and management, as well as organized labor, accept the importance of physical examinations, both preplacement and periodic, as a basis for conserving the effectiveness of the individual at work. In accordance with these newer concepts, constant surveillance of the worker must be maintained, with follow-up examinations at periodic intervals, at transfer to another job and on return to work after any illness. Indeed, as industrial medicine enters the second half of the century, it is not unlikely that the pre-placement physical examination will become the keystone of the entire nation's adult preventive-medicine program.

Undoubtedly, the most significant development in industrial medicine in the last fifty years is the growth of industrial hygiene, with its emphasis on the prevention of occupational diseases. Accidents are dramatic events in which cause and effect are relatively easily determined. Occupational illness, on the other hand, is subtle in origin, insidious in character and chronic in its development. Its relation to exposure to an industrial chemical or to an unfavorable occupational environment is frequently extremely difficult to establish. However, it became apparent soon after the passage of the workmen's-compensation laws that modifications to include occupational diseases would have to be made. In the last twenty years the majority of industrial states have passed such additional laws making occupational disease compensable. This quickened the employer's interest in averting the illnesses, just as the earlier legislation had prompted them to prevent accidents. As a result, industrial hygiene was instituted.

In order successfully to analyze and control a hazardous occupation, it was found necessary to utilize the skills of not only the physician but the engineer, the chemist, the sanitation expert, the epidemiologist and a host of others. The potential poisons and unfavorable environmental conditions in industry are so protean, extensive and changeable as to require the participation of virtually all the medical and sanitary sciences in the field of industrial hygiene. The literature relating to industrial health and environmental control not only appears in journals specifically concerned with those subjects but is scattered throughout all the scientific publications. Although progress has been made in the toxicology of industrial poisons, the outstanding achievement has been the determination of general principles of control, applicable to all industrial processes. It is the culminating feat of industrial medicine that through its resourcefulness some of the most virulent poisons known to man are handled daily in large quantities by large numbers of people without any ill effects. Over the past several decades, the number of published reports on various specific occupational diseases, such as silicosis and lead and mercury poisoning,

has constantly decreased, showing that measures of control have been successfully undertaken. The hazards of atomic radiation and the use of beryllium, which are essentially outgrowths of the last world war, now predominate in the literature, indicating that there are still many unsolved problems. The application of our known industrial hygiene technics permits safe operation with these materials, but the industrial hygienists are still working to reduce the cost of the control measures. The physicians meanwhile are actively attempting to define the deleterious effects of these two industrial hazards and to strengthen the host factor in combating them. If the experience of the past half-century is any measure, there is no doubt that success will be achieved.

In reviewing these advances it is worth noting that preventive medicine in industry has not developed in the same manner in Europe, although Europe had the initial advantage. There were several reasons that American industry took the lead. One was the recognition that industry, in order to make technical progress, must work with hazardous materials. At the same time, it was difficult to establish under the workmen's compensation laws whether or not exposure to hazardous substances or adverse physical conditions was related to illness. Workers quickly became wary of any threat to their health in the plant, especially since they had to bear the cost of such illness unless and until causality could be decided. Furthermore, when cases were established as being industrially caused, the cost to industry was likely to be great. The uncertainty and the excessive cost of these cases, both to management and workers, acted as a powerful lever toward creating safe working environments.

Safe atmospheric limits for the various industrial poisons were defined through the co-operative efforts of engineers, chemists and physicians. Official and nonofficial lists of the more common industrial poisons and their safe tolerance limits have been published and revised through the last several decades. The experimental and toxicologic laboratories have been of inestimable help in determining in advance whether, and to what extent, a new industrial substance or process was potentially harmful. These maximum allowable concentrations do not represent absolute safety for the worker but are engineering benchmarks that if attained assure him reasonable protection. Technical achievements in the handling of industrial poisons during the past fifty years are too numerous to be detailed. It can be said that by and large we know the effects of the more common ones; most importantly, we have mastered the principles of preventive technics, based chiefly on engineering measures, with preventive medicine as an adjunct to the entire safety program.

Another element in the growing emphasis on preventive medicine in industry has been the attitude of the American worker concerning his own feeling and desire to care for himself. Under our rapidly expanding industrial economy, the better worker was attracted to the job that offered the most healthful and most comfortable working surroundings. Furthermore, he had no background of relying on a medical-care program to compensate him in the event of illness. The one major exception has been the workmen's-compensation system itself, but it does not provide adequate recompense for the losses entailed by sickness. The American worker, aware of his own dignity and worth, is insistent on better working conditions and not on a social-security plan. Here is probably the most potent of the intangible factors stimulating and promoting preventive medicine in industry.

Employers' interest in medical matters was and is limited to the work environment. Workers, on the other hand, have shown through the years an increasing awareness of the economic problems of total medical care and have turned to industry for assistance in its solution. Industry has not resisted, as is indicated by the multitude of voluntary health plans for nonoccupational sickness benefits, hospitals, surgical emergencies and so forth that are in existence. In the last decade, particularly under the influence of the wage stabilization of World War II, workers have been receiving health benefits that are considered part of their wages. In an increasing number of states this has been placed on a legislative basis. Even though the forces that promoted these health plans have slackened the trend remains, since it represents an intrinsic need. The development of union-sponsored group health services with industry's active co-operation is inevitable and will probably gain momentum in the coming years.

Role of Government in Industrial Medicine

Throughout the course of industrial medicine's progress, our national, state and local governments have played an active part, particularly in the fields of education and research. The first decade of the century ushered in a whole body of social legislation including, besides the workmen's-compensation laws, state laws controlling working hours in factories and mines, sanitation, working conditions of women and children and other matters related to industrial health. The scope of existing laws for factory inspection and regulation was enlarged. Physicians commissioned by state or municipal governments began to inspect hazardous working conditions, opening the way for government guidance and assistance throughout industrial medicine. Various departments of the Federal government — notably the Division of Industrial Hygiene of the United States Public Health Service, the Division of Labor Standards of the United States Department of Labor and the United States Bureau of

Mines — functioned with increasing success in the preventive medical field, especially in the last fifteen years. Responsive to industry's urgent needs for manpower conservation during and since World War II, the public agencies have emphasized more than ever the preventive aspects of their activities. The chief functions of the public agencies have been the investigation of specific occupational hazards, not in any one plant but on an industry-wide basis, the recruiting and training of personnel and the provision of advisory services and grants-in-aid to the various states for educational purposes. In the most recently organized and widely discussed of any industry — atomic energy — the entire health program is of course administered by an arm of the national government: the Division of Biology and Medicine of the United States Atomic Energy Commission.

With the unique exception of atomic energy, all industries today retain control of and responsibility for industrial health. Until very recently the public agencies took the initiative in the broader aspects of industrial health, leaving each individual industry to carry out in its own narrow confines whatever medical program seemed to fit its needs. During the last few years, however, not the government but industry, with its newly awakened recognition of responsibility, has become the spearhead in the broader functions of industrial medicine. Industries, both individually and in groups, now support a number of educational projects, fellowships and research grants by means of which specialists in various aspects of industrial medicine can be trained. Examples are the industry-financed programs at New York University and at the Universities of Michigan, Pittsburgh and Cincinnati.

The work of organizing and administering industrial medical programs has become in itself a specialty in the last ten years. Experience amassed in the development of medical departments and programs in the large industries provided the foundation for administering medical programs in the smaller industrial units, which now comprise the majority of our industrial organizations. Valuable information concerning staff, personnel, facilities and other factors of plant medical services had to be applied in order to bring the most efficient and least expensive medical practices into industry as a whole. The skills thus developed combined to form the special practice of organization and administration of industrial health programs.

The precise function of medicine in the soaring industrial economy of these last fifty years has never been satisfactorily defined. The demands made upon the industrial physician are as diversified and as ever-changing as our industrial society itself. This is exemplified by the multiplicity of professions and skills that are necessary complements to the medical sciences. Engineering and chemistry, toxicology and research, law, administration, economics, individual and group psychology, education, labor relations and social welfare are only a few of the ancillary knowledges essential to modern industrial medical practice. So vast, in fact, is the array of activities participated in by the plant physician that it is difficult to state what training and experience he should have in order to qualify as a specialist. The industrial physicians themselves, seeking to fix their place in relation to the rest of organized medicine, have united in ever-growing numbers of professional organizations. They formed the American Association of Industrial Physicians and Surgeons, then allied themselves as the Industrial Hygiene Section of the American Public Health Association. They participated in the formation of the American Industrial Hygiene Association. In 1937 a Council on Industrial Health was created by the American Medical Association. Finally, only four years ago, the American Academy of Occupational Medicine was organized and a movement is at present on foot to recognize industrial medicine as a formally constituted specialty.

To what bounds the ever-expanding field of industrial medicine may ultimately extend is a subject for speculation. At the beginning of this second half of the present century, it is difficult, if not impossible, properly to orient industrial medical activities in the framework of conventional medical practice. The trend, however, is unquestionably toward industrial medicine's becoming a social science rather than a fragment of traditional medicine and surgery practiced on industry's premises. Its scope and importance, far from diminishing since the close of World War II, are greater today than ever, as industry continues to expand and the need for conserving manpower persists. In the next fifty years, more and more medical practice will be encompassed within the industrial framework; the individual's occupation may become the focal point for health programs affecting every area of his life, the community and the nation.

Correction. In the fifty-year Medical Progress report "Medicine as a Social Instrument: Public Health" by Dr. Haven Emerson, which appeared in the February 22 issue of the *Journal*, the figure "100,000" in the next to the last line in the second column on page 292 should be changed to read "10,000."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

FOUNDED BY RICHARD C. CABOT

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CASE 37171

PRESENTATION OF CASE

A fifty-one-year-old woman entered the hospital complaining of progressive swelling of the neck.

For several years prior to admission she had tired easily and had been excessively nervous and emotionally unstable. For thirteen years before entry she noted episodic bouts of flushing and hyperhidrosis of the right face, neck and upper chest. These spells characteristically were related to periods of emotional distress and warm weather, lasted thirty to sixty minutes and left the patient feeling weak and faint. For a year prior to admission she experienced increased exertional dyspnea, becoming short of breath on climbing one flight of stairs. There was no associated tachycardia, but at times she was aware of the sensation of her pulse in her ears. Seven months prior to admission she developed a cold that failed to clear up and since then had hoarseness and an irritative cough that occasionally produced yellowish sputum. Shortly after this she noticed swelling of the neck, which was first called to her attention by a friend. At this time she also noted that food caught in her throat and at times spilled into her airway.

Six months before entry she consulted her physician, who reported a basal metabolic rate of +26. She was given sedatives and 8 small pills, which she stated were a thiourea derivative, to take daily. She took the medication until ten days before entry. On this regimen her nervousness decreased, and she was recently told that her basal metabolic rate was −8. Two months before admission she noticed that her hair was becoming drier and her features coarser, especially about the eyes and lips. One month later she developed swelling of the submaxillary salivary glands. There had been no significant change in weight.

The past history revealed that she had received radium treatments twenty years previously for a pelvic tumor, the nature of which was not known. She had had no menses since then. Six years previously she developed urinary retention, which was treated by cystotomy; after that she had some frequency and nocturia three to four times. She had had "anemia" for an undisclosed length of time that allegedly did not respond to treatment. She had had chronic constipation for many years, but during periods of distress she had diarrhea.

Physical examination revealed a well developed, well nourished, pallid woman with coarse, dry skin and hair. The features, especially the lips and tongue, were thickened. There was no lid-lag, tremor or myasthenia. The neck showed a firm but not hard diffusely enlarged thyroid gland of about three times normal size, with irregularities of the surface. The pyramidal lobe was palpable. The submaxillary glands were enlarged, soft, smooth and nontender. A millet-seed-sized node was felt, medial to the upper lobe. The heart, lungs and abdomen were negative. There was no visible evidence of a cervix. The ankle jerks were absent and knee jerks were obtainable on reinforcement. The pupils reacted to light and distance.

The temperature was 98.6°F., the pulse 80 and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

The urine (catheter specimen) had a specific gravity of 1.010, and gave a + test for albumin; the sediment contained 3 white blood cells and ++ bacteria per high-power field, which proved to be *B. coli* on culture. The hemoglobin was 12.2 gm. and the white-cell count 9000, with a normal differential. The sedimentation rate was 60 mm. in sixty minutes. The basal metabolic rate was −26 per cent. The blood Hinton test was positive on two occasions and the blood Wassermann test was negative. A lumbar puncture revealed no abnormal findings. The gold sol was 0000111000 and the spinal-fluid protein was 41 mg. per 100 cc. An x-ray study of the chest showed slight prominence of the left ventricle. There was no substernal extension of the thyroid gland. Direct visualization of the larynx revealed paresis of the right vocal cord.

The hospital course was uneventful except for a daily rise in temperature to 100°F. for the first ten days. She was given penicillin, 35,000 units twice each day for eleven days, and potassium iodide solution, 10 drops daily. A tracer dose of 100 microcuries of radioactive iodine showed an uptake of 60 per cent in twenty-four hours.

On the thirteenth hospital day during anesthesia induction (with ether) for an operation the patient experienced a precipitous fall in blood pressure to 40 systolic, 30 diastolic. The pulse fell to 46. Anesthesia was discontinued, and the patient recovered without other incident. An electrocardiogram was reported as showing low T waves in all leads. On the twentieth hospital day an operation was performed.

Differential Diagnosis

Dr. J. H. Means*: I assume the operation was on the goiter. The differential diagnosis is: What kind of goiter was removed from this woman's neck?

There are many interesting points in the history that I should like to review. This goiter developed rather rapidly in a fifty-one-year-old woman — at least six months before entry it had not been noted by the patient, and then a friend noticed it; shortly thereafter the goiter became large enough to cause pressure, disturbing swallowing. The slight vocal-cord palsy noted on physical examination suggests that the goiter may have involved the laryngeal nerve also.

Whenever a goiter is present, one wonders about the state of the patient's thyroid function. Was this patient hyperthyroid, euthyroid or hypothyroid? It is important in the differential diagnosis of goiters to know whether the patients have ever been spontaneously hyperthyroid or hypothyroid. One metabolic rate of +26 is not enough on which to make a diagnosis of hyperthyroidism; the patient was nervous, and she may have had ordinary "jitters" when the basal metabolic rate was done. I once had a basal metabolic rate of +40, but on that occasion, when on the way to have the test made, I met somebody with whom I became angry; that raised my metabolic rate. Nor does the fact that she was given thiourea necessarily mean that she was hyperthyroid. Some physicians give thiourea for some forms of thyroiditis, but we do not believe it does any good in such conditions. It is more likely that she was thought to have had hyperthyroidism and was given the antithyroid drug to correct that. At any rate, she took eight pills — I do not know what the dose was — from six months before entry until ten days before entry. That after six months on thiourea she had become grossly myxedematous impresses me; I should not have expected such gross myxedema in a thyrotoxic person. I think the most likely possibility is that the patient was not thyrotoxic but euthyroid when the antithyroid drug was given and that a state of true hypothyroidism was induced by the drug.

When the patient was in the hospital, she was given potassium iodide — I do not know why. Potassium iodide is usually given to thyrotoxic patients in preparation for surgery. Then she was given a tracer dose of radioactive iodine and the uptake was at the upper border of normal. An uptake from 60 per cent up indicates hyperthyroidism and from 50 per cent down is normal; in between is the great area of doubt. The patient did not have a decrease in iodine uptake. The only way I can reconcile a good iodine uptake with a −26 basal metabolic rate and myxedema is to say that the thyroid gland could collect the iodine but it could not turn it into hormone; that could have been due to the drug. It would have been interesting to have determinations of the protein-bound iodine of the blood.

There is one point in the past history that I should like to clear up. Twenty years before admission, the patient's pelvis was cleaned out — uterus, ovaries and so forth — so that she had an induced menopause at the age of thirty-one. Six years later, or thereabouts, she began having episodes of strange unilateral flushing and hyperhidrosis of the right face, neck and upper chest that lasted for a short time and left her weak and faint. What on earth may this have been? I do not believe it was Horner's syndrome; there was nothing else to go with it. Cervical sympathetic stimulation would have had to be present to produce this kind of picture — and then there would have been other symptoms and signs. I must confess that I asked Dr. Stanley Cobb what might produce such symptoms. He thought they were very bizarre and suggested that they were probably not unilateral but really bilateral. However, he recalled a patient who had had unilateral sweating as a result of a lesion in the hypothalamus. If it had been bilateral and had occurred sooner, I would have thought it was merely a menopausal phenomenon.

I was intrigued by the submaxillary salivary adenitis. The enlargement of the salivary glands may have been due to the thiourea; we have had cases of salivary-gland inflammation following the administration of antithyroid drugs. The other possibility is that not a salivary gland but lymph nodes in the region were enlarged.

The only comment I can make about the radium treatment is to ask: Could it have been the cause of a subsequent cancer? Dr. Joseph C. Aub tells us so often that whenever we give radium treatment we may be laying the foundation for further cancer that I am hypersensitive in this regard.

On physical examination the findings were clear-cut and definite; the patient was myxedematous and had a firm but not stony-hard thyroid gland, diffusely enlarged to three times normal size. Since three times normal size is not very large, the gland must have had a positive extension to press on the esophagus and interfere with swallowing. There were irregularities of the surface that are found with multiple adenomas or cysts, but they are also associated with neoplasms and with chronic types of thyroiditis, particularly Hashimoto's struma. The enlargement of the pyramidal lobe also favors Hashimoto's struma, although it may also be enlarged in Graves' disease. I am sure the patient did not have Graves' disease.

That the blood Hinton test was positive on two occasions and the Wassermann negative is intriguing. I wondered if the false positive Hinton test might have been a clue to the kind of goiter, and I looked up causes of false positive reactions in the

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literature. I was amazed at how inadequately the subject was treated. However, a variety of infections other than syphilis, as well as liver diseases that produce a disturbance in plasma protein, may give rise to false positive Hinton tests. I think it may be a clue to the diagnosis, but I do not know how to interpret it.

On the thirteenth hospital day, while being given ether, the patient went into temporary shock with bradycardia. The anesthetist whom I questioned about this said that it could not have been due to ether but Pentothal or cyclopropane, if either had been given, could have caused it. I do not know the cause of the reaction.

I think the picture this patient presented was that of a spontaneous goiter plus the effects of an antithyroid drug. What kind of goiter could this have been? It was not an endemic or sporadic colloid goiter, nor a hyperplastic goiter; therefore it must have been either neoplastic, chronic-inflammatory or amyloid. In the chronic inflammatory group one thinks first of Hashimoto's struma. Then there is Riedel's struma, which is the woody type of thyroiditis that grows almost like cancer. Tuberculosis, syphilis, as suggested by the two positive Hinton tests, and sarcoidosis may involve the thyroid, but I have never seen such cases. The only one of the inflammatory group that I think is probable is Hashimoto's struma.

In the group of neoplasms are the benign and malignant neoplasms. If it was malignant, was it primary in the thyroid or metastatic to the thyroid? Hypernephromas have metastasized to the thyroid. I have heard of a case of rectal cancer that had metastasized to the thyroid, and carcinoma of the larynx may extend into the thyroid. However, I shall dispose of metastatic disease because it is so very rare. Of course, the thyroid may be involved in a lymphomatous process; there are even a certain number of goiters that appear to be lymphomatous without any lymphoma elsewhere.

Primary cancer of the thyroid may be highly malignant, may grow very rapidly and may produce pressure symptoms. If it was primary carcinoma, I should expect it to be harder and more firmly fixed than this was. Then there are follicular adenocarcinomas, papillary adenocarcinomas, sarcomas and so forth. I cannot find any good arguments for any of these, but I am inclined to believe that if this goiter was neoplastic it was malignant.

I cannot decide between Hashimoto's struma and malignant tumor of the thyroid gland; I do not believe anyone could do more than guess. The way to make the diagnosis is to do a biopsy; if I were handling such a case, that is what I should require.

Clinical Diagnosis

Thyrotoxicosis.

Dr. Means' Diagnosis

Hashimoto's struma or malignant tumor of the thyroid.

Anatomical Diagnosis

Hashimoto's struma.

Pathological Discussion

Dr. Benjamin Castleman: The preoperative diagnosis was thyrotoxicosis, which Dr. Means ruled out entirely.

Dr. Means: I tried to.

Dr. Castleman: At the time of operation the surgeon found a very diffuse enlargement of the gland (about three times the normal), which was resected; I shall show you a photograph of it (Fig. 1). This is, as you see, a diffuse process; even the isthmus was involved. The next slide of the cut surface shows a distinct lobular pattern with a uniform appearance (Fig. 2). There were no areas of necrosis or hemorrhage, which you might expect in a malignant tumor. This was a highly characteristic Hashimoto struma, with lymphoid tissue and germinal centers replacing much of the parenchyma. Many of the remaining acinar cells were swollen, and since there was a 60-percent uptake of radioactive iodine in this patient I suppose this is pretty good evidence that the remaining acini, both the normal-appearing ones and those that appeared to be in an early stage of atrophy, may still have been active. In fact, it was

Figure 1.

shown by Parmley and Hellwig* and confirmed by Dr. Austin Vickery in our laboratory that in Hashimoto's struma there really is an increase in the amount of acinar tissue in addition to the lymphoid tissue.

DR. FARAHE MALOOF: The diagnoses that we entertained were Hashimoto's struma and carcinoma. I favored the former. It is difficult to say whether or not the slightly elevated twenty-four-hour uptake (60 per cent) of radioactive iodine was due to the antithyroid drug. The patient was myxedematous and had an elevated twenty-four-hour uptake of radioactive iodine that certainly suggested a goitrogenic effect. I know of a patient with sarcoidosis, a nodular goiter and a persistently high basal metabolic rate whose radioactive iodine and protein-bound-iodine studies revealed that she was euthyroid. She was given propylthiouracil, 300 mg. a day, for four months without any change in the basal metabolic rate, symptoms or weight but with a change in the forty-eight-hour excretion of radioactive iodine from 60 per cent to only 16 per cent. It appears that in the latter patient the antithyroid drug did change the radioactive-iodine studies in four months.

FIGURE 2.

DR. MEANS: There are two points I should like to have cleared up. Was she ever thyrotoxic, and was the myxedema the result of the disease or of the antithyroid drug or both? Hashimoto's struma, which destroys parenchyma, can produce myxedema. If she had not had the antithyroid drug and had become myxedematous, I should have been certain that the goiter was a Hashimoto struma. But since she had had an antithyroid drug I was a little puzzled about which was the actual cause of the athyreosis: disease, drug or both.

DR. MALOOF: The way to determine whether the myxedema was due to the antithyroid drug or not would have been to stop the antithyroid drug, to remove only part of the gland and to observe the patient by repeating the studies.

DR. MEANS: Was she thyrotoxic to begin with?

DR. MALOOF: That is difficult to answer; however, I do not believe so.

*Parmley, C. C., and Hellwig, C. A. Lymphadenoid goiter: its differentiation from chronic thyroiditis. *Arch. Surg.* 53:190-198, 1946.

CASE 37172†

PRESENTATION OF CASE

First admission. A forty-three-year-old man was admitted to the hospital in coma.

For one year prior to admission the patient had vague epigastric pain associated with much gas and belching. Over the five weeks previous to entry he had attacks of vomiting and finally he was unable even to keep liquids down. On the day prior to entry he had two convulsions and after the last passed into deep coma.

He had had generalized psoriasis for twenty years and he had a history of recurrent attacks of chills and fever, said to be malaria, from three to thirteen years of age. He drank about one pint of whiskey daily.

Physical examination showed an extremely dehydrated, flushed, comatose man with a generalized psoriatic eruption. There was some tenderness in the epigastrium.

The temperature was 100°F. and the pulse and respirations normal. The blood pressure was 135 systolic, 90 diastolic.

Urinalysis, blood studies and chemical determinations confirmed the clinical findings of dehydration. A gastrointestinal series showed an obstruction at the pylorus, with no barium passing into the duodenum. An x-ray film of the chest was negative. Plain films of the abdomen showed a number of calcified lymph nodes.

On the sixteenth day, after a period of routine preparation, a posterior gastroenterostomy and appendectomy were performed. The operative note stated: "There was extensive edema of the duodenum, pylorus, head of the pancreas and gastrocolic ligament, with many old and fresh inflammatory adhesions. There was almost certainly an acute ulcer on the posterior aspect of the first portion of the duodenum adherent to the pancreas."

†Presented before the American College of Surgeons in Boston, October 25, 1950.

He improved slowly, regained his appetite, strength and some weight and was discharged on the thirty-eighth postoperative day. Prior to discharge, an x-ray film taken after a barium swallow showed satisfactory function of the gastroenterostomy stoma, with a small amount of barium trickling through a deformed duodenum.

Second admission (twelve years later). The patient had come to the Out Patient Department once six years before this because of a small ulcerating lesion along the hairline. He did not return for treatment. In the interim the lesion on the forehead had slowly spread to involve the anterior half of the scalp, with loss of hair. Biopsy of the lesion showed Bowen's disease. The involved skin was excised and the area covered with a split-thickness skin graft. He was discharged on the twenty-fourth hospital day. In the twelve-year interval there had been no recurrence of the gastrointestinal complaints. At this admission bilateral inguinal hernias were present.

Third admission (nine months later). Four months before admission, the patient entered another hospital because of a sudden attack of severe abdominal pain and vomiting in the middle of the night. The pain apparently was not relieved by milk or alkali and subsided gradually after six or seven hours. There had been three such attacks in the two months before this; they seemed to follow dietary indiscretions. He left the hospital against advice at the end of nine days. In the three months following discharge he suffered recurring episodes of abdominal pain, anorexia and constipation, and lost thirty pounds. In the subsequent month he regained his appetite, was free of pain and was regaining some weight. The inguinal hernias that had been present for many years were no longer easily controllable.

Physical examination showed a well healed grafted area on the scalp, bilateral reducible indirect inguinal hernias and a liver palpable two fingerbreadths below the costal margin.

Urinalysis was normal. The blood hemoglobin was 12.5 gm. and the white-cell count 7500. The total protein, the chloride, a van den Bergh test, the nonprotein nitrogen and a cephalin-flocculation test were normal. A barium-enema examination was negative. A gastrointestinal series was as before, with the distal stomach and duodenum not visualized. The stoma was patent. The liver and spleen were enlarged.

A right-inguinal herniorrhaphy was performed, and the patient was discharged on the eighteenth hospital day.

Fourth admission (two months later — for repair of left-inguinal hernia). In the interim he had been well. Physical examination was the same as on the previous admission except for a questionable yellowish-bronze tinge of the skin. The patient claimed this had been present for many years and attributed it to the psoriasis. There was no history of clay-colored stools or dark urine.

On the second hospital day a left-inguinal herniorrhaphy was performed. On the following day definite jaundice was present. The van den Bergh reaction was 2.5 mg. direct, with a total of 3.3 mg. per 100 cc. The total protein, albumin-globulin ratio, cephalin flocculation, thymol turbidity and nonprotein nitrogen were within normal limits. On the sixth postoperative day the patient suddenly developed a shaking chill with a temperature of 102.5°F. but with no pain. The liver was palpable five fingerbreadths and the spleen three fingerbreadths below the costal margin. They were not tender. The jaundice was a little deeper. On careful questioning it was now elicited that the patient had had three brief attacks of chills with fever in the period covering two years before admission, but none in the last five months. Although he had been a heavy drinker, he stated that he had stopped drinking four years before entry.

A roentgenogram of the chest showed an irregular area of increased density, with questionable cavitation in the left first and second intercostal spaces. There was also an old fibrotic process in the left apex. A Graham test showed no visualization of the gall bladder. A gastrointestinal series was as before. A metastatic bone series was negative.

Examination of the blood disclosed a hemoglobin of 11.5 gm. and a red-cell count of 3,900,000. A blood smear was negative for malarial parasites. The alkaline phosphatase was 33.6 units, the urine urobilinogen 1.25 Ehrlich units, the cholesterol 184 mg. and the cholesterol esters 110 mg. per 100 cc.; the bromsulfalein was 20 per cent and the prothrombin time 17 seconds (normal, 15 seconds). A liver biopsy showed acute cholangiolitis. After recovery from the brief chill the patient became afebrile and remained so for the rest of this admission. He regained some strength and was discharged on the twentieth day, with instructions to return in one month. Prior to discharge a chest plate showed some clearing of the density in the left upper lobe.

Fifth admission (one month later). During the month at home he had felt well and gained seven pounds. Physical examination was much as before. There was an icteric tinge of the sclera, a nontender liver palpable just above the iliac crest and an enlarged spleen palpable three fingerbreadths below the costal margin. The temperature, pulse, respirations and blood pressure were normal.

The alkaline phosphatase was 30 Bodansky units per 100 cc.; the cephalin-flocculation test was ++ in twenty-four and forty-eight hours. The nonprotein nitrogen, chloride, total protein, albumin-globulin ratio, prothrombin time and urinalysis were normal. The hemoglobin was 11.5 gm.

On the eleventh hospital day a laparotomy disclosed a large, hard mass in the head of the pancreas; several biopsies of this mass showed chronic pancreatitis. The common bile duct could be probed down to the mass in the pancreas but not beyond; above this the duct was dilated. Cholecystectomy and choledochostomy with drainage were performed. In view of the length of time consumed in exploration it was decided to defer any further operative procedure to a later day.

The immediate postoperative course was relatively smooth. There was a large amount of bile drainage from the T-tube. The stools remained clay colored. On the seventh postoperative day the nonprotein nitrogen was 74 mg. per 100 cc. and the van den Bergh reaction less than 0.4 mg. direct and 0.6 mg. per 100 cc. total; the chloride was 93 and the sodium 123.5 milliequiv. per liter. The patient appeared to be deteriorating somewhat, and in spite of a normal temperature the white-cell count was 50,000, with a normal differential. With increased intravenous therapy he showed remarkable subjective improvement and a return to a normal electrolyte balance. At the end of one month the nonprotein nitrogen was 44 mg., the amylase 74 units, the lipase 2.64 cc. and the total protein 5.9 gm. per 100 cc. The chloride concentration was 100 milliequiv. and the potassium 4.7 milliequiv. per liter. He continued to do well in spite of a drainage of approximately 1500 cc. of bile daily. His appetite was good and he gained about six pounds over three weeks. The stools were light brown. Attempts to clamp the T-tube were not successful, and a cholangiogram showed obstruction in the common bile duct, with only a small amount of the dye reaching the duodenum after some hours. The common bile duct and hepatic radicles were dilated (Fig. 1). Numerous amylase determinations varied between 88 and 108 units per 100 cc. The electrolytes remained within normal limits. He was discharged on the seventieth hospital day on a diet including bile-replacement therapy, to return in two months for re-evaluation in view of possible further surgical therapy. On the day prior to discharge the total protein was 7.47 gm., with an albumin-globulin ratio of 1.9, the nonprotein nitrogen 33 mg., the amylase 93 units and the hemoglobin 10.8 gm. per 100 cc.

Final admission (nine months later). Three months previous to entry the T-tube became blocked, but after irrigation bile again flowed readily through the tube. During the following three months the patient's appetite had decreased, with a loss of strength and a weight loss of thirty pounds. For the ten days prior to admission the T-tube had not drained well.

On physical examination no icterus was noted. The heart and lungs were negative. There was a draining T-tube in the right upper quadrant of the abdomen. The liver was percussed four finger-breadths below the costal margin; the tip of the spleen was barely palpable.

The temperature was 101°F., the pulse 100 and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

Urinalysis was normal. Examination of the blood revealed a hemoglobin of 10 gm. and a white-cell count of 11,600. The stools were clay-colored and tests for bile were negative. The total protein was 6.41 gm., the albumin 2.59 gm. and the globulin 3.82 gm. per 100 cc.; the amylase was 28 units and the nonprotein nitrogen 26 mg. per 100 cc. The prothrombin time was 22 seconds (normal, 17 seconds), the cephalin-flocculation test ++ in twenty-four and forty-eight hours and the phosphatase 10.6 Bodansky units per 100 cc. An x-ray film of the chest showed that since the last examination many areas of increased density had appeared in each upper lobe and in at least one of the lower lobes, with some changes in the right middle lobe. There was also some loculated fluid in the right pleural cavity, laterally and posteriorly (Fig. 2). Cholangiograms showed no change from the previous examination.

FIGURE 1.

The course was rapidly downhill, with a temperature up to 101°F., and extreme loss of weight. The patient died on the twenty-first hospital day.

Differential Diagnosis

Dr. Francis D. Moore*: This is the long, complicated case of a man who came into the hospital in coma thirteen years before the final admission, re-entered several times for other conditions, including Bowen's disease and a pulmonary lesion, and finally died with a pancreatic lesion.

Before I start my discussion I should like to ask Dr. Castleman to look at the patient's record and tell me the values for the blood and urine sugars.

Dr. Benjamin Castleman: Three of ten urine examinations showed a green reaction for sugar on the first admission. The blood sugar was 121 mg. per 100 cc.

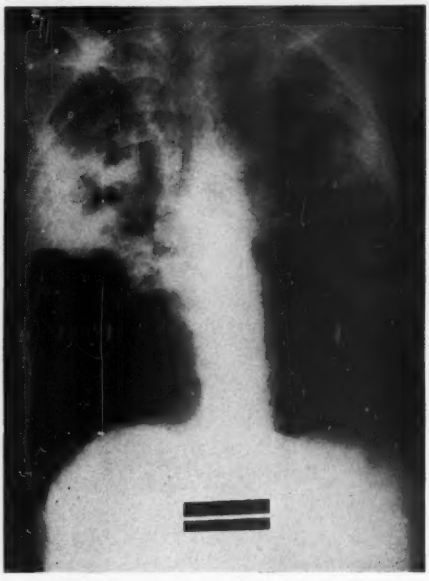

Figure 2.

Dr. Moore: A blood sugar of 121 mg. is abnormal. If it was not done while he was in the phase of acute dehydration, it is suggestive of diabetes mellitus.

Dr. Sosman, would you tell us about the x-ray findings?

Dr. Merrill Sosman†: The only x-ray films available are those taken a year before those done during the final admission. The stomach shows a well functioning gastroenterostomy but no filling of the antrum. This may have been resected, shrunken or constricted by disease or tumor. The cholangiogram (Fig. 1) shows marked dilatation of hepatic and common ducts, with both deformity and constriction just above the ampulla. There is no spilling into the duodenum but there is also no invasion to indicate carcinoma of the pancreas. We would interpret the findings as due to a mass constricting and obstructing the lower end of the common bile duct.

Dr. Moore: Was there calcification in the pancreas?

Dr. Sosman: Yes; the film also shows multiple small areas of calcification that presumably are in the pancreas itself, which I believe are pancreatic calculi. Many other films show the same arrangement. I should like to raise the question whether these were the calcifications reported as calcified lymph nodes twelve years previously.

Dr. Moore: Is there any density in the liver or spleen to suggest hemochromatosis?

Dr. Sosman: The liver density does not appear to be abnormal. The films of the chest taken a year before the final admission show only slight involvement of the left subclavicular area — very small areas of infiltration. A year later (Fig. 2) there is a remarkable change — extensive involvement of both upper lobes, spreading into the apex of the right lower lobe, in all probability, and what appears to be a cavity in the center of this mass on the right. There is consolidation of both upper lobes but none in the lower lobes except, possibly, at the apex of the right lower lobe. This suggests tuberculosis. The heart is small.

Dr. Moore: Does the heart look like Addison's disease?

Dr. Sosman: Very definitely, I would say.

Dr. Moore: Do you see any calcification in the adrenal glands?

Dr. Sosman: No; it is lower and spread diffusely all over the left kidney, not in one area at the top of the kidney.

Dr. Moore: As usual, the Radiology Department has given us some information that only makes the problem more complicated.

The patient had Bowen's disease, as demonstrated pathologically. My understanding of Bowen's disease is that it is a premalignant skin lesion. I should like to ask Dr. Castleman if he would define Bowen's disease and if he has ever seen metastatic disease associated with such a lesion.

Dr. Castleman: It is usually defined as carcinoma in situ of the skin, which very rarely metastasizes. If it does metastasize, it does so very late in the course of the disease when it is no longer in situ, usually only to the regional lymph nodes.

Dr. Moore: I shall then dismiss Bowen's disease from further discussion.

The calcified lymph nodes reported in the abdominal film taken during the first admission suggest that at some time in the past the patient had had a bovine type of tuberculosis; that may be significant.

*Surgeon-in-chief, Peter Bent Brigham Hospital.
†Radiologist-in-chief, Peter Bent Brigham Hospital.

The obstruction of the pylorus, with no barium passing through during the barium meal, suggests a duodenal ulcer. The obstruction could have been due to a lesion on the gastric side of the pylorus, such as a carcinoma or even a benign ulcer, or it could have been due to disease in the pancreas. It is of interest that there is a high incidence of motor disorder in the upper gastrointestinal tract, manifested by obstruction, in acute and subacute pancreatitis. It is impossible to say what the lesion causing the obstruction may have been without looking at the x-ray films, which apparently are not available now.

The surgeon's operative notes sound as if he were trying to talk himself into the diagnosis of a duodenal ulcer. Since it is almost impossible to palpate a posterior-wall duodenal ulcer in such an inflamed duodenum, I believe that the lesion as a whole looked like that of a duodenal ulcer but that I ought not to consider that proof that the patient had a duodenal ulcer.

Dr. Castleman: The surgeon was Dr. Edward D. Churchill.

Dr. Moore: That is helpful information but still not proof that this was ulcer! We have seen patients with benign lesions or with cancer in the head of the pancreas who had inflammatory lesions around the duodenum that looked like duodenal ulcer. The first good historical evidence that I am not dealing with a duodenal ulcer appeared four months before the third admission. The severe pain occurring at night in discrete attacks lasting for six or seven hours, not relieved by milk or alkali, suggests recurrent attacks of acute pancreatitis rather than duodenal ulcer. In the next three months he had recurrent attacks of abdominal pain, anorexia and constipation and lost thirty pounds in weight. Subsequently his appetite was good, he gained weight and he was free of pain. All this is compatible with chronic pancreatitis, with characteristic remissions and exacerbations. Patients with chronic pancreatitis (especially those who have calcification in the pancreas) often lose weight, may have fatty stools and occasionally have a superimposed diabetes.

X-ray films taken at the time of the third admission showed enlargement of the liver and of the spleen. I do not believe that both the hepatomegaly and splenomegaly can be accounted for solely on the basis of extrahepatic biliary disease, even though this may produce hepatomegaly and biliary cirrhosis; when splenomegaly is present, one has to think in terms of the blood diseases or of intrahepatic disease with obstruction of the portal circulation. In this case I must consider the possibility that the pancreatitis may have been caused by a thrombosis of the splenic vein.

Three months later a laparotomy was performed, and a hard mass was found in the head of the pancreas from which a biopsy was taken. The biopsy showed only chronic pancreatitis; this does not rule out cancer. Pancreatic biopsy at best is unsatisfactory; cancer may be present in the pancreas with pancreatitis surrounding it. The light-brown stools noted at the time of the final admission indicate that the common duct had opened up again and was putting bile through after a period of complete obstruction. This effectively excluded carcinoma of the head of the pancreas, which so characteristically produces an increasing jaundice that never remits. This patient's jaundice disappeared twice.

For the first time, during the third admission, the liver was noted to be enlarged, but the liver-function tests were normal. He had been a chronic alcoholic but claimed that he had stopped drinking about four years previously. About two months later the alkaline phosphatase was markedly elevated, suggesting extrahepatic biliary-tract obstruction. Intrinsic parenchymatous liver disease in the form of acute hepatitis can produce elevation of the alkaline phosphatase but not as a rule so marked an elevation as this was. The urobilinogen of 1.25 Ehrlich units indicates that some bile was getting into the gastrointestinal tract. The bromsulfalein retention of 20 per cent shows that parenchymatous liver disease was present. A liver biopsy was done. Was it a punch biopsy, and did it show any evidence of hemochromatosis?

Dr. Castleman: It was a punch biopsy, and it did not show any evidence of hemochromatosis; it was the sort of biopsy specimen that is seen in infection.

Dr. Moore: It would be interesting to know if the patient had esophageal varices. If they were present, it would be helpful.

It is interesting that this patient had pigmentation, a low sodium concentration and tuberculosis. Did he have Addison's disease? I should like to point out that he had three operations without

going into shock or anything that resembled shock; as a test of adrenal function, there is nothing quite so revealing as a surgical procedure. He did not have Addison's disease.

I am sure that when Dr. Castleman described the skin as yellowish-bronze tinged he did so with a great deal of relish, as all sorts of conditions can produce pigmentation of the skin, among them hemochromatosis. In addition, he had a pulmonary lesion and may have had gall-bladder disease, which also suggests hemochromatosis. Patients with hemochromatosis often develop tuberculosis or possibly have a decreased resistance to tuberculosis. Hemochromatosis is an attractive possibility. He had a large liver and spleen as well as pigmentation. About 25 per cent of patients with hemochromatosis do have diabetes. In about 10 per cent there is epigastric pain not related to meals and usually accredited to pancreatitis. The punch biopsy of the liver is very much against this diagnosis. I cannot exclude it, however.

Why was this patient operated on? He had a large spleen and liver, a chronic disease, weight loss and intermittent abdominal pain. I suppose he was operated on to exclude the possibility of an operable cancer. The chance that a common-duct stone was present must have also been considered by the surgeon.

Were gallstones found?

DR. CASTLEMAN: The patient did not have gallstones.

DR. MOORE: That leaves me with several possibilities. The best bet is chronic pancreatitis with calcification and recurrent attacks of acute pancreatitis, with obstruction of the common duct and splenic-vein thrombosis. As a second possibility Addison's disease or hemochromatosis is attractive but unlikely. My diagnosis will be chronic pancreatitis, with recurrent acute attacks, obstruction of the bile flow, chronic cirrhosis of the liver, possibly alcoholic, splenomegaly due to cirrhosis or to splenic-vein thrombosis, and, as a terminal episode, pulmonary tuberculosis.

DR. GORDON SCANNELL: Dr. Moore is right about the reason for operating on the patient. The patient was not jaundiced at the time of operation. The right upper quadrant was badly scarred and when the gall bladder was unavoidably traumatized in the effort to demonstrate the common duct, it was necessary to remove it. We had hoped to find a stone in the duct but could only demonstrate obstruction at the level of the pancreas. The duodenum was opened and the papilla of Vater identified; a probe was passed upward for about a centimeter until an obstruction was met. We could not establish communication with the upper end of the tract, although I may point out again that the patient was not jaundiced at this time. A pancreatic biopsy was done in the hope of establishing the diagnosis, but, as so frequently happens, this was not helpful.

The statement that the postoperative course was relatively smooth is interesting. The patient really did not do very well; at no time was he in sufficiently good condition to warrant another operation, assuming that we had wished to do one. Had we been able to salvage the gall bladder that might have allowed us to create an internal biliary fistula. As it was, he drained to the outside and returned to the clinic whenever his tube plugged. A major attempt at reconstruction could not be seriously considered.

CLINICAL DIAGNOSES

Tuberculosis of lungs, far advanced.
Chronic pancreatitis.

DR. MOORE'S DIAGNOSES

Chronic pancreatitis with acute episodes.
Obstruction of the common bile duct, due to pancreatitis, with cirrhosis of the liver (? alcoholic).
Splenic-vein thrombosis.
Pulmonary tuberculosis.

ANATOMICAL DIAGNOSES

Pancreatitis, chronic, fibrosing, severe.
Pulmonary tuberculosis, bilateral, caseo-cavernous type, severe.
Biliary obstruction, common bile duct, extrinsic.
Bile-duct dilatation, common and hepatic bile ducts, severe.
Biliary cirrhosis, liver, slight.
Choledocho-cutaneous fistula.
Tuberculosis of mediastinal and retroperitoneal lymph nodes, liver and left adrenal gland.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The patient did die of tuberculosis. The lungs were filled with caseous cavitating tuberculosis. The lymph nodes in the mediastinum were also involved with tuberculosis, as

were the lymph nodes in the abdomen. There were a few miliary tubercles in the liver and none in the kidneys. One adrenal gland was completely replaced by caseous tuberculosis but the other was not. I doubt that even mild Addisonian symptoms could result from involvement of one adrenal gland.

DR. MOORE: Was it the left adrenal gland that was tuberculous?

DR. CASTLEMAN: Yes; but it was not calcified. I should like to show you a diagram of the abdomen (Fig. 3). You can see the fistulous tract,

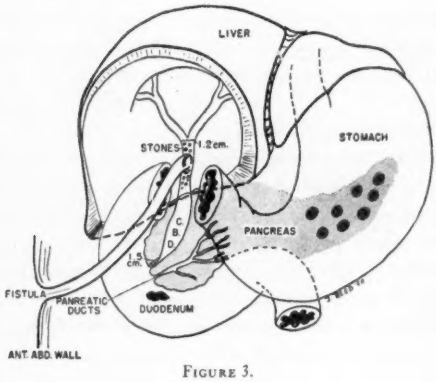

FIGURE 3.

in which there is a tube leading to the common bile duct about 1.5 cm. below the bifurcation into the hepatic ducts, which are markedly dilated. There are a few stones in the common bile duct, which is also dilated down to the papilla, where it suddenly becomes very narrow. We were unable to put a small probe through that orifice. The pancreatic duct is also narrowed at its orifice but is patent throughout the rest of the pancreas. The pancreas itself was stony-hard, and scattered over its surface were hard white nodules, not really so discrete as they seem in the diagram. They extended over the entire pancreas — not only in the tail, as shown. On section most of the parenchyma was replaced by fibrous tissue, and these nodules seemed to be fibrous also. The gall bladder was absent, and in its bed were large numbers of dense fibrous adhesions between it and the first portion of the duodenum, the pylorus, the hepatic flexure and the head of the pancreas. These viscera, or parts of viscera, were so adherent that it was difficult to dissect out the individual organs in that area. However, after extensive dissection we were still unable to find any evidence of an old duodenal ulcer. We could not rule it out, however. It could have been healed enough not to be easily seen. Microscopical examination of the pancreas showed a tremendous amount of fibrosis throughout and an extensive chronic inflammatory reaction. The pancreatic duct was dilated with secretions, which in places were calcified.

We have then a chronic sclerosing pancreatitis, which probably narrowed the openings of the bile and pancreatic ducts. I do not believe we can be sure of the original cause of the pancreatitis. My explanation is that perhaps there really was a duodenal ulcer that had penetrated the head of the pancreas, as was described at the first operation, and had produced a pancreatitis that had progressed slowly until the patient's death. Amylase determinations would fit that. We were unable to find any evidence of a carcinoma.

DR. MOORE: Why was the spleen big?

DR. CASTLEMAN: The spleen weighed only 350 gm. and was not abnormal microscopically. The portal and splenic veins were normal. The liver weighed only 1600 gm. and showed slight biliary cirrhosis, indicating that the drainage fistula had decompressed the biliary tree quite well.

DR. ERNEST CRAIGE: No hemochromatosis?

DR. CASTLEMAN: No.

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CIVITAS HIPPOCRATICA

THE Massachusetts Medical Society, now in the one hundred and seventieth year of its corporate existence, can boast of the unique distinction of having assumed at least partial responsibility for two old and internationally recognized medical institutions. It has owned and published since 1921 its *Journal*, originally established as the *New England Journal of Medicine and Surgery* in 1812. It has more recently recognized the needs of the Boston Medical Library, now in its seventy-sixth year, and has responded by allocating to it $5.00 annually from the dues of each active fellow. The increasing use of the Library in recent years, particularly notable since the arrangement with the Society went into effect, is indicated on the accompanying chart (Fig. 1).

In return for this payment each fellow of the Society automatically becomes a "Massachusetts Medical Society member" of the Library, with all the privileges of membership except that of belonging to the Corporation. The privilege of carrying on the latter responsibility appertains to the fellows of the Library — a privilege for which they gladly pay an additional $15 a year, although the majority of them are also fellows of the Massachusetts Medical Society.

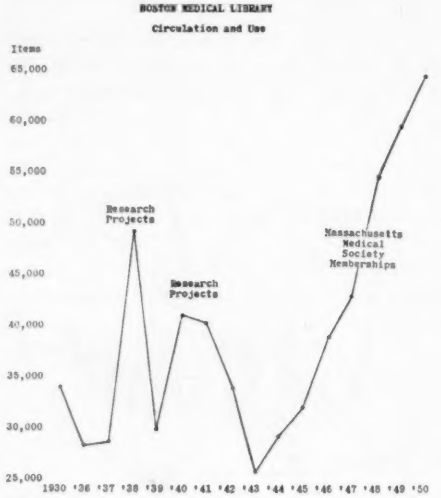


FIGURE 1.

It is natural that confusion should have arisen concerning this dual responsibility of the fellows of the Library—and that some of them, unaware of their exalted position, should have sought to escape its pecuniary obligations. Fortunately, these are relatively few in number; the majority, aware that the contribution of the Massachusetts Medical Society was intended to supplement and not to supersede the income derived from the original fellowship, have remained true to their trust. May their tribe increase!

The Library merits this confidence, and its support must be continued and augmented at any cost. Those of its members who have made their personal contributions grudgingly, on the basis of their deriving no personal benefit from it, must ask themselves what personal benefit they receive from the United Community Fund, the Red Cross, the Salvation Army or any other philanthropic en-

terprise to which they contribute. They are not buying personal service in supporting the Library, but they are broadening that stream of knowledge by which their entire medical existence is made to flourish.

The Boston Medical Library is the third largest in the United States, pre-eminent in fields related to the history of medicine and possessing one of the world's finest collections of both ancient and current medical periodicals. Not a single book that is added to its shelves (now patently inadequate to house the collection) is purchased from current income; special funds are available for this purpose. All of the Library's revenue from dues is applied to its various operating expenses — including service, which, also inadequate, will be increased in scope as the income improves.

The final decision of the Massachusetts Medical Society to establish its new headquarters next to the Library, which continues to house the offices of the *Journal*, suggests that former possibilities have become present probabilities. With its admirable postgraduate teaching program so well established and with these other institutions so permanently a part of the family, the leadership of the Society in the development of a true Academy of Medicine becomes almost inevitable.

Until the next phase develops, which must include the costly construction necessary for the final utilization of the stack space still vacant in the building, the devoted fellows of the Library will continue to play their extraordinary part in holding the organization together. May they remain conscious of the obligations that they have so willingly assumed!

PRIVATE WEALTH AND PUBLIC WELFARE

The Fifth Annual Report of the Life Insurance Medical Research Fund has recently been published. It states that nearly $3,500,000 has been contributed by about 150 life-insurance companies in the past five years. Of this amount over $3,000,000 has been paid or appropriated for grants and fellowships entirely devoted to research on cardiovascular diseases. One hundred and forty-seven research programs and 129 research fellowships have been supported. Free enterprise is thus sharing its wealth in a private capacity, as well as publicly via its taxes. Medical schools are thus assured a financial reserve with which to resist government control while accepting government aid to medicine, which now totals nearly three times the sum available from philanthropic foundations. Physicians concerned with the day-to-day care of the sick are increasingly grateful for the resultant new tools for cure or for comfort.

Also recently issued is the Twentieth Anniversary Review of the Josiah Macy, Jr., Foundation, detailing the expenditure of about $3,000,000 on approximately 800 projects. Especially interesting is the role in medicine chosen by this purely private philanthropic foundation. Since astronomical goals have been set up for expenditure on medical and allied research ($200,000,000 annually by 1957), private philanthropy can hope to bear only a small part (5 per cent) of the financial burden. However, it may assume a much larger share of responsibility at the frontiers of knowledge by taking advantage of its flexibility and freedom of operation to support the exploration of new or currently unpopular fields. A result of this philosophy is the Macy Foundation's conference program, already a proved idea-catalyst in medical thinking.

In this time of rapid change, with the threat of the welfare state at hand, it is necessary to preserve not only individual freedom but also individual responsibility, and to fit them into the unfolding social pattern of the future. The donor of the Macy Fund expressed this idea in 1930 at the time of its establishment: "Experience seems to show that in an enlightened democracy, private organized philanthropy serves the purpose of human welfare best, not by replacing functions which rightfully should be supported by our communities, but by investigating, testing, and demonstrating the value of newer organized ideas for sustained undertakings, from which may gradually emerge social functions which in turn should be taken over and maintained by the public."

PREVENTIVE MEDICINE UNIT: ARMY MEDICAL SERVICE

The emergence of a preventive medicine unit of company size during the Korean conflict proves the

ability of the Army Medical Service to capitalize on a successful experiment for an improved permanent organization. During World War II, malaria control units were improvised in order to cope with the specific disease. However, as might be expected during the course of a global war, such units sometimes found themselves in places where malaria was not a problem. In Europe, during the winter months of 1944, malaria control was hardly a pressing problem, but trench foot developed in such proportions among riflemen as to constitute a significant handicap to the military effort. In the adaptation of available personnel to existing circumstances, some members of malaria control units, along with other unemployed specialists, were assigned to the control of trench foot. One of the most illuminating studies of the subject that came out of the war was undertaken by a gas-warfare officer and an entomologist unacquainted with the specific problems of trench foot. Their important attributes were a thorough acquaintance with the scientific method and the application of science to the problems of groups of people — whether those problems were due to frost or heat, vehicular accidents, chemicals or insects.

In the Pacific Theater it was a malaria control unit that worked out the measures needed to reduce the rat population in Manila to a point where it no longer constituted a major health menace. Subsequently, "malaria control units" engaged in a variety of activities, some as far removed from malaria as venereal disease. It gradually became clear that a specialized team is no more necessary for the control of each major disease than is a medical specialist for each cure. What is needed is a knowledge of the principles of science in general and of some of the appropriate basic medical and public-health disciplines. The responsible policy makers in the military hierarchy have been wise enough to see that the same team that could successfully cope with the preventive problems of malaria, venereal disease and trench foot could probably cope with scrub typhus or tsutsugamushi fever. The challenge is not very different from that which confronts the medical staff of a station or general hospital, which collectively is expected to treat these and a multiplicity of other diseases.

At present the new preventive-medicine companies are composed of six officers, one warrant officer and 59 enlisted men. In Korea they are assigned not only to malaria control and survey but to the general objective of controlling insect-borne and waterborne diseases. If the complexion of the war should change significantly, the functions of the preventive medical company could very likely change apace. It is most encouraging to see the same ingenuity and adaptability that characterizes this nation's peacetime industrial performance operating in the planning and policies of military medicine.

CREATURE COMFORT

Scientists of the University of Wisconsin, according to a feature story emanating from the News Service of that institution of learning, have been turning their attention to the heat-regulating systems of various fur-bearing animals. Those of the frigid zone, it has been discovered, apparently possess heat-producing mechanisms that are superior to those with which the animals of more clement climates are equipped. As Jacob learned, however, when he robbed Esau of Isaac's blessing, a fur coat also helps.

The lemming, that small rodent of circumpolar distribution, accustomed to extremely low temperatures, has in addition to its other thermoregulatory devices a body build designed to discourage the dispersal of heat from the surface area, for the animal is more nearly spherical in shape than are most mammals, with very short, heavily furred legs. One lemming, in fact, under laboratory observation, died of heat prostration at an air temperature of only 77 degrees. Such an outcome, of course, may be attributable to the lack of an ocean into which to plunge in large numbers.

Among the arctic and subarctic animals that are being studied in regard to their capacity for remaining comfortable under adverse circumstances are the whistling marmot, the fox, the ground squirrel and the mouse. Of the temperature-maintaining factors mentioned, perhaps the one that contributes most strikingly to this desirable state of affairs is the physiologic ability of such animals to produce heat, for, to paraphrase the Wisconsin zoologists, it takes more than a mink coat to keep a minx warm, whether in Alaska or in the District of Columbia.

A Bath paper, of recent date, informs us that within the last three months the waitress at the Cross Keys inn, Orange-grove, in that city, has from time to time, complained of pains and aches in different parts of her person; and within the last month, not fewer than thirty-two needles have been extracted from her knees. — London Lancet.

Boston M. & S. J., *April 30, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BOWERS — George F. H. Bowers, M.D., of Newton, died on April 1. He was in his sixty-eighth year.

Dr. Bowers received his degree from Harvard Medical School in 1911. He was a member of the New England Pediatric Society and a fellow of the American Medical Association.

Two sisters and two grandchildren survive.

LANGILL — Morton H. Langill, M.D., of Worcester, died on March 30. He was in his sixty-eighth year.

Dr. Langill received his degree from Dartmouth Medical School in 1910. He was a member of the New England Roentgen Ray Society and the American College of Radiology and a fellow of the American Medical Association.

A sister survives.

O'BRIEN — Joseph V. O'Brien, M.D., of Dorchester, died on February 16. He was in his forty-fourth year.

Dr. O'Brien received his degree from Harvard Medical School in 1935. He served on the staffs of Boston City, St. Margaret's, Milton and Cambridge hospitals, and on the surgical staff of the Carney Hospital from 1938 until his last illness.

His mother and two sisters survive.

ROZANSKI — Frank S. Rozanski, M.D., of Auburn, died on March 5. He was in his thirty-ninth year.

Dr. Rozanski received his degree from Hahnemann Medical College, Philadelphia, in 1937. He formerly served on the staffs of St. Vincent and Fairlawn hospitals. He was a member of the American Medical Association and the American Psychiatric Association.

His widow, three sons, a daughter, five brothers and two sisters survive.

SNOW — Frank W. Snow, M.D., of Newburyport, died on March 10. He was in his seventy-third year.

Dr. Snow received his degree from Harvard Medical School in 1902. He was a fellow of the American Medical Association.

There are no immediate survivors.

WHITEHOUSE — Eugene D. Whitehouse, M.D., of Newcastle, Maine, formerly of Quincy, died on March 28. He was in his seventy-fourth year.

Dr. Whitehouse received his degree from Harvard Medical School in 1905. He was the founder of the Whitehouse Maternity Hospital in Wollaston, and served on the staff of Quincy Hospital. He retired in 1946.

A son, a daughter and five grandchildren survive.

BOSTON MEDICAL LIBRARY

ANNUAL MEETING

The postponed annual meeting of the corporation of the Boston Medical Library will be held at 4:30 p.m., on May 21, at the Hotel Statler.

It is hoped that the change of time and place to coincide with those of the annual meeting of the Council of the Massachusetts Medical Society will bring forth an unusually large attendance.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

MITCHELL — William H. Mitchell, M.D., died on March 2, at the age of 83. He was born in Woodsville, New Hampshire, the son of Abram and Angeline Eastman Mitchell.

Dr. Mitchell had been a resident of Loudon, New Hampshire, since 1896, having moved there from Suncook. He retired from the practice of medicine five years ago.

Dr. Mitchell was educated at Pembroke Academy and Dartmouth Medical School. He was a member of the New Hampshire Medical Society, Blazing Star Lodge, A. F. & A. M., and the Scottish Rite.

Survivors include a nephew, John S. Mitchell of Kittery, Maine, and several cousins.

SWETT — Eddy Benjamin Swett, M.D., died on February 22, 1951. He was born in Nashua, New Hampshire, November 3, 1867, the son of Newell S. and Lucy (Abbott) Swett.

A graduate of Harvard Medical School, class of 1899, he began practicing medicine in Marlboro, Massachusetts, in that year. He removed to Goffstown Center (now Grasmere), New Hampshire, in September, 1891, where he practiced until his retirement a few years ago. In 1892 he married Ettie Elizabeth Ballard, of Marlboro, Massachusetts, who died in 1947.

Dr. Swett served in the Medical Corps during World War I and was active in the Reserves until his retirement as a Lieutenant-Colonel. He was a traditional country doctor, who traveled by horse and buggy, — and on snowshoes in the winter months — until his return from military service, when he acquired a motorcycle, which he used until 1936, when his eyesight became impaired. He had been totally blind for several years prior to his death.

He was on the staff of the Hillsborough County General Hospital since its founding and was physician-in-charge of the Hillsborough County Farm for over forty years.

Dr. Swett was a member of St. Matthew's Episcopal Church of Goffstown, of which he was the senior warden for many years. He was also a member of the Hillsborough County and New Hampshire medical societies; a charter member of Wesley Wyman post, No. 16, American Legion; past commander and past district deputy of District No. 4; a member of Webster lodge No. 24, I.O.O.F., of Goffstown; and a Golden Sheaf member of Junior Grange, No. 150, of Grasmere.

He is survived by five daughters: Mrs. Merrill G. Sumner of Manchester, Mrs. Webster L. Simons of Hanau, Germany, Mrs. Bert Anderson of Clearwater, Florida, Mrs. C. Gardner Caverly of Ipswich, Massachusetts, and Miss Barbara Swett of Grasmere; a son, Donald B. Swett of West Hartford, Connecticut; a brother, Arthur N. Swett of Mt. Vernon, N. Y.; seventeen grandchildren and three great-grandchildren and a cousin, Mrs. Bertha Perrin of Berne, Texas.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

THE ALCOHOLIC

From the earliest historical times, the drunkard has been a familiar figure, a source of misery and distress to himself and his family, often a burdensome responsibility to the community, and usually the despair of those who would restore him to a sober and productive life. He has been treated with high humor, rejection, disinterest, abuse, neglect and incarceration. To many "morally" minded, he has meant, and still does mean, the vagrant, the bum and the weak-willed. However, in recent years, as a result of research and medical leadership, the public and various professional groups have been persuaded that the alcoholic is a sick person, worthy of and amenable to successful treatment and rehabilitation.

Many alcoholics have been started on the road to recovery by the living example of Alcoholics Anonymous, with their some 100,000 successfully rehabilitated members. Many have also been helped by the pioneer private and public clinics, which have courageously stuck by their convictions.

A better understanding of the disease can be attained when one differentiates the heavy drinker and the "occasional drunk" and the sick alcoholic. The heavy drinker and the "occasional drunk" become inebriated entirely *by choice* and with malice aforethought, at times and on occasions selected by them as appropriate for such behavior. In our present-day society, such occasions do occur with some frequency and are quite acceptable in some social circles. On the other hand, the sick alcoholic has *lost the power of choice* in the matter of drinking. For him, choice is no longer possible in regard to drinking, to the amount consumed, the effects of that amount on him and the occasion. Furthermore, the condition can only be *arrested — never cured* to the point where he can again resume controlled or so-called normal drinking.

Research being carried on throughout the world on the pathologic physiology of alcoholism and its etiology and treatment reveals that there are multiple and complex factors involved. It cannot as yet be clearly stated why or how a person becomes an alcoholic. However, factors of physiologic instability, personality inadequacy, maladjusted interpersonal relations, overwhelming social and economic stresses and spiritual and moral conflicts can often be traced through the life history of those who have become alcoholics. Frequently, the specific damaging effects of alcohol overlie the earlier or "trigger" illness and complicate the whole by a sort of chain reaction in which alcohol is ultimately used to relieve the symptoms that it caused, so that there is no end to the drinking.

JOHN C. AYRES, M.D.
Division of Alcoholism

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY, 1951

RÉSUMÉ

DISEASE	FEBRUARY 1951	FEBRUARY 1950	SEVEN-YEAR MEDIAN
Chancroid	5	2	2
Chicken pox	2068	2043	2043
Diphtheria	5	13	21
Dog bite	521	584	575
Dysentery, bacillary	2	6	9
German measles	84	143	143
Gonorrhea	169	182	303
Granuloma inguinale	0	0	0
Lymphogranuloma venereum	2	0	1
Malaria	0	0	8
Measles	1352	611	1877
Meningitis, meningococcal	9	5	9
Meningitis, Pfeiffer-bacillus	2	4	3
Meningitis, pneumococcal	4	6	4
Meningitis, staphylococcal	1	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	4	1	5
Mumps	1429	916	1091
Poliomyelitis	1	0	0
Salmonellosis	1	4	4
Scarlet fever	629	508	706
Syphilis	114	94	271
Tuberculosis, pulmonary	165	233	200
Tuberculosis, other forms	11	12	12
Typhoid fever	0	3	2
Undulant fever	3	1	1
Whooping cough	244	518	410

COMMENT

The only diseases notably above the seven-year median for this month are mumps and undulant fever.

Diseases whose prevalence is below the seven-year median include diphtheria, bacillary dysentery, German measles, measles, salmonellosis, scarlet fever, typhoid fever and whooping cough.

The 5 cases of diphtheria is the lowest number ever reported for this month. February is also the eighteenth consecutive month for which the number of cases of diphtheria reported was less than for the corresponding month of the previous year.

The 244 cases of whooping cough is the lowest number reported for February since 1917.

The number of cases of mumps is the highest for this month in three years.

Although still below the median, scarlet fever is tending upward. This is the fifth consecutive month that it has been higher than the previous year.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Cambridge, 3; Easton, 1; Waltham, 1; total 5.

Dysentery, amebic, was reported from: Newton, 1; total, 1.

Dysentery, bacillary, was reported from: Worcester, 2; total, 2.

Encephalitis, infectious, was reported from: Cambridge, 1; total, 1.

Hepatitis, infectious, was reported from: Haverhill, 1; total, 1.

Meningitis, meningococcal, was reported from: Andover, 1; Beverly, 1; Billerica, 2; Boston, 1; Brockton, 1; Framingham, 1; Lowell, 1; Tewksbury, 1; total, 9.

Meningitis, Pfeiffer-bacillus, was reported from: Lowell, 1; Mansfield, 1; total, 2.

Meningitis, pneumococcal, was reported from: Boston, 1; Framingham, 1; Springfield, 1; Wakefield, 1; total, 4.

Meningitis, staphylococcal, was reported from: Holyoke, 1; total, 1.

Meningitis, undetermined, was reported from: Easton, 1; Mendon, 1; Taunton, 1; Webster, 1; total, 4.

Poliomyelitis was reported from: Lynn, 1; total, 1.

Salmonellosis was reported from: Belmont, 1; total, 1.

Septic sore throat was reported from: Adams, 5; Boston, 1; Duxbury, 1; Easthampton, 1; Fitchburg, 1; New Bedford, 1; Shirley, 1; total, 11.

Tetanus was reported from: Fall River, 1; total, 1.

Trichinosis was reported from: Groton, 1; North Attleboro, 1; Norwood, 2; total, 4.

Undulant fever was reported from: Cambridge, 1; North Andover, 1; Northbridge, 1; total, 3.

CORRESPONDENCE

ORAL MONILIASIS FOLLOWING ANTIBIOTIC THERAPY—A WARNING

To the Editor: The development of antibiotics has been one of the great achievements of modern medicine. Infectious processes that in the past ended fatally or caused permanent infirmities are practically unknown since the advent of penicillin and its successors.

However, the indiscriminate use of these "wonder" drugs is not without great danger to the patient. Generalized sensitivity reactions and even anaphylactic shock following the use of an antibiotic have been reported repeatedly.

The normal bacterial flora of the body is altered during the use of an antibiotic. For example, pure cultures of gram-negative bacteria are often isolated from the throat of patients who are receiving penicillin therapy, whereas the normal flora of the throat is gram-positive. Staphylococcic meningitis has developed in patients receiving streptomycin for *Hemophilus-influenzae* meningitis.

The normal mouth and pharynx harbor many organisms that in small numbers are not pathogenic and cause no symptoms but are part of the natural flora. Chief among these are spirochetes, fusiform bacilli and organisms of the monilia group. If normal conditions are disturbed and favor the growth of any one of these, active growth begins and an infection due to this organism may take place.

About two years ago, when antibiotic troches became popular, we began to see patients with generalized stomatitis, with and without exudate, following this therapy. These patients present a clinical picture varying from that of an uncomplicated inflammatory reaction to that of a generalized mycotic infection resembling the various stages of so-called "black hairy tongue." Involvement of the pharynx and tonsils is not uncommon.

The mucous membrane may be covered with a whitish exudate resembling whipped cream, a dirty-brown exudate or a black, "hairy" covering. All three types of exudate may be present in the same patient.

Careful bacteriologic studies of these patients invariably reveal abundant organisms of the *Monilia albicans* group.

Within the last three months we have seen this complication in patients who have been receiving systemic aureomycin or Chloromycetin therapy.

Early withdrawal of the offending drug usually results in a disappearance of the exudate, improvement of clinical symptoms and a return of the bacterial flora to normal. If the mycotic infection is well established, however, specific fungicidal therapy must be used.

A few of these patients whose fungous infection has been untreated have presented the picture of advanced mycotic disease with involvement of the mouth, tongue, pharynx and tonsils. One of them had been unable to eat solid food for several weeks, had lost 40 pounds in weight and was markedly debilitated.

Another complication that might conceivably result if such patients are not treated adequately is pulmonary moniliasis.

In short, local antibiotic therapy of the mouth and throat with troches and lozenges is to be discouraged, as it is frequently followed by a generalized fungous infection. This oral complication is becoming increasingly more frequent in patients receiving systemic aureomycin or Chloromycetin therapy.

The offending drug should be immediately withdrawn from patients presenting a picture suggestive of this complication. Specific fungicidal therapy should be used if evidence of mycotic infection persists for more than forty-eight hours after the antibiotic has been withdrawn.

ANITA MANGIARACINE
Bacteriologist, Massachusetts Eye and Ear Infirmary
Boston

CANCER COMMISSION OF HARVARD UNIVERSITY LABORATORY OF PATHOLOGY

To the Editor: On Friday, March 23, the Laboratory of Pathology of the Harvard Cancer Commission and the Massachusetts State Tumor Diagnosis Service moved from their former quarters in Harvard Medical School, Building E–2, to the new Cancer Research Institute of the New England Deaconess Hospital. The address is 194 Pilgrim Road, Boston, Massachusetts. The telephone number is Aspinwall 7-4620.

The staff will continue as previously and the service will be uninterrupted.

It is believed that in the new quarters the Laboratory can even more effectively aid the physicians of the Commonwealth in their efforts to bring cancer under control.

SHIELDS WARREN, M.D.
Boston

"MYOCARDITIS OF UNDETERMINED ORIGIN"

To the Editor: I question the validity of the explanation of sudden deaths as claimed in the brief paper entitled "Myocarditis of Undetermined Origin: A Cause of Unexpected Death" in the *Journal* of March 15, 1951, inasmuch as I have frequently seen these same lesions in hearts of patients dead of varying diseases in which there had been no suddenly or even rapidly developing cardiac symptoms, and no sudden death, as well as in hearts of patients dying with the progressive cardiac decompensation of chronic nonvalvular heart disease, in which I long have had an interest. These lesions seem, by reason of their histologic appearance, to have developed some considerable time prior to death. Just what part they play as a cause of myocardial insufficiency remains, for me at least, an enigma. If more extensive examinations of the heart muscle were made I feel sure that these lesions would be seen in a steadily increasing number of hearts.

HENRY A. CHRISTIAN, M.D.
Brookline, Massachusetts

NOTICES

ANNOUNCEMENTS

Dr. Edward A. Edwards announces the removal of his office to 330 Dartmouth Street, Boston.

Dr. Andrew R. MacAusland announces the removal of his office on May 1 to 218 Commonwealth Avenue, Boston.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The annual dinner and meeting of the Massachusetts Society of Examining Physicians will be held at the Harvard Club in Boston at 6:30 p.m. on May 2.

Dr. Herbert Conway, associate professor of clinical surgery at Cornell Medical School, will present a paper on "The Therapy of Burns, with Critical Evaluation of ACTH," illustrated with films.

All interested physicians are invited to attend.

NEW ENGLAND HOSPITAL

The monthly clinical conference and meeting of the staff of the New England Hospital will be held in the conference room of the hospital on Thursday, May 3, at 7:15 p.m. Dr. Ann Wight will speak on the subject "ACTH in Burn Therapy." Dr. Annella Brown will be chairman.

SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of May is as follows:

Thursday, May 3.
12 m. Allergy Conference in the Staff Conference Room. Dr. H. B. Tillman.

Saturday, May 5.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Radiology Conference (topic to be announced) in the Staff Conference Room. Dr. John W. Turner.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds in the Staff Conference Room.

Wednesday, May 9.
12:15 p.m. Psychosomatic Medicine Conference in the Staff Conference Room on the subject "Therapies in Psychiatric Problems." Dr. Calvert Stein.

Thursday, May 10.
12:15 p.m. Staff Meeting in the Staff Room.

Saturday, May 12.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Seminar on Surgical Principles in the Staff Conference Room on the subject "Children's Surgery." Dr. F. C. Leonard.
11 a.m.–12 m. Clinicopathological Conference in the Staff Conference Room.

Tuesday, May 15.
8:30 p.m. Guest Speaker Conference in the Staff Conference Room on the subject "The Rh Factor and its Relation to Intragroup Transfusion Reactions and Hemolytic Disease of the Newborn." Dr. Arthur W. Wright, professor of pathology and bacteriology, Albany Medical College and pathologist-in-chief, Albany Hospital, Albany, New York.

Saturday, May 19.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Pathology Conference in the Staff Conference Room on the subject "Practical Laboratory Aids in the Diagnosis of Parasitic Diseases." Dr. William Kaufmann.
11 a.m.–12 m. Medical-Death Review in the Staff Conference Room.

Wednesday, May 23.
12:15 p.m. Pediatric Conference (topic to be announced) in the Staff Conference Room. Dr. H. H. Shuman.

Saturday, May 26.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Seminar on Surgical Principles in the Staff Conference Room on the subject "Surgery of the Uterus and Perineum." Dr. Lewis Whiting.
11 a.m.–12 m. Surgical-Death Review in the Staff Conference Room.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheatre of Building D of the Harvard Medical School on Tuesday, May 8, at 8 p.m.

The program, presented by the Department of Biological Chemistry (Professor A. Baird Hastings presiding), will be as follows:

Some Properties of the Cellular Electron Transmitting System. Eric G. Ball.
Ion and Hormone Effects on Carbohydrate Metabolism in vitro. A. Baird Hastings and C. T. Teng.
Metabolic Studies with Radioglycerol. Manfred L. Karnovsky and Lewis I. Gidez.
In-vitro Studies on Fetal Metabolism. Claude A. Villee.

AMERICAN RADIUM SOCIETY

The 33rd annual meeting of the American Radium Society will be held in Atlantic City, New Jersey, June 7–9. The meeting will feature a symposium on tumors of the head and neck. The treatment of cancer with drugs and by biochemical means will also be discussed. The Janeway Lecture, the highest award of the society, will be delivered by Dr. H. Dabney Kerr, of Iowa City, Iowa.

BOSTON DISPENSARY

An all-day scientific meeting, sponsored by the proctologic staff of the Boston Dispensary, will be held on May 5 at the Hotel Kenmore in Boston. All physicians interested in proctology are invited to attend. Reservations may be obtained from Dr. John F. Keane, 122 Commonwealth Avenue, Boston.

BOSTON UNIVERSITY SCHOOL OF MEDICINE ALUMNI ASSOCIATION

The Scientific Session of the annual meeting of the Alumni Association of the Boston University School of Medicine will take place on May 4, in the auditorium of the Boston University School of Medicine, 80 East Concord Street, Boston. The program is arranged in honor of the tenth anniversary of Dr. Chester S. Keefer's directorship of the Evans Memorial Department for Clinical Research and Preventive Medicine, Massachusetts Memorial Hospitals.

MORNING
(10:00 a.m.–12:00 m.)

Speculations Concerning the Etiology of Polycythemia Vera. Dr. William B. Castle, professor of medicine, Harvard Medical School.
Current Concepts of the Mechanism of Cardiac Asthma. Dr. John Curry, associate professor of medicine, Georgetown University.
Influenza and Pneumonia. Dr. Maxwell Finland, associate professor of medicine, Harvard Medical School.

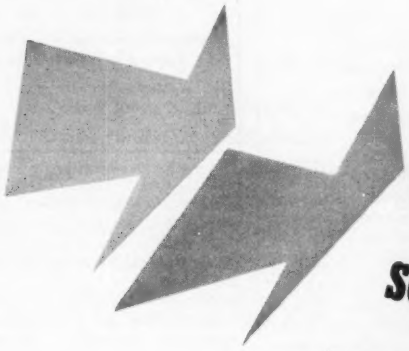
AFTERNOON
(2:00–4:00 p.m.)

Body Water and Its Subdivisions. Dr. J. Murray Steele, professor of medicine, New York University.
Mental Gymnastics and Mental Gyrations. Dr. Frederick Yonkman, medical director, Ciba Pharmaceutical Products, Inc., and lecturer in pharmacology, Columbia University College of Physicians and Surgeons.
Some Advances in Therapeutic Research. Dr. Chester S. Keefer, Wade Professor of Medicine, Boston University School of Medicine.

SOCIETY MEETINGS AND CONFERENCES

APRIL 28. Boston City Hospital Alumni Association. Page 614, issue of April 19.
APRIL 28. American Psychosomatic Society. Page 198, issue of February 1.
APRIL 28. Alumni Association, Long Island College of Medicine. Page 458, issue of March 22.
MAY 1. Hampden District Medical Society. Page 614, issue of April 19.
MAY 2. Massachusetts Society of Examining Physicians. Page 655.
MAY 3. New England Hospital. Notice above.
MAY 3–26. Springfield Hospital. Notice above.
MAY 4. Boston University School of Medicine Alumni Association. Notice above.
MAY 5. Boston Dispensary. Notice above.
MAY 7–11. National League of Nursing Education. Page 384, issue of March 8.
MAY 8. New England Society of Anesthesiologists. Page 614, issue of April 19.
MAY 8. Harvard Medical Society. Notice above.
MAY 9. Norfolk District Medical Society. Page 629, issue of October 19.
MAY 9–11. American College of Surgeons. Page 614, issue of April 19.
MAY 10. Differential Diagnosis and Treatment of Poliomyelitis. Dr. Louis Weinstein. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
MAY 16. New England Obstetrical and Gynecological Society. Hillcrest Country Club, Leicester, Massachusetts.
MAY 16–18. American Association of Genito-Urinary Surgeons. Page 160, issue of January 25.
MAY 21–25. International Society of Orthopaedic and Traumatic Surgery. Page 422, issue of March 15.
MAY 22–24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

(Notices concluded on page xxi)



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Editorial: J.A.M.A. *135*:576, Nov. 1, 1947.

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Griggs, D. E., and Johns, V. J.: California Med. *69*:133, Aug. 1948.

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Harding, F. E.: West. J. Surg. Obst. & Gynec. 52:31 (Jan.) 1944

"All patients (53) described a sense of well-being" following "Premarin" therapy for menopausal symptoms.

Neustaedter, T.: Am. J. Obst. & Gynec. 46:530 (Oct.) 1943.

"It ('Premarin') gives to the patient a feeling of well-being."

Glass, S. J., and Rosenblum, G.: J. Clin. Endocrinol. 3:95 (Feb.) 1943

"General tonic effects were noteworthy and the greatest percentage of patients who expressed clear-cut preferences for any drug designated 'Premarin.'"

Perloff, W. H.: Am. J. Obst. & Gynec. 58:684 (Oct.) 1949.

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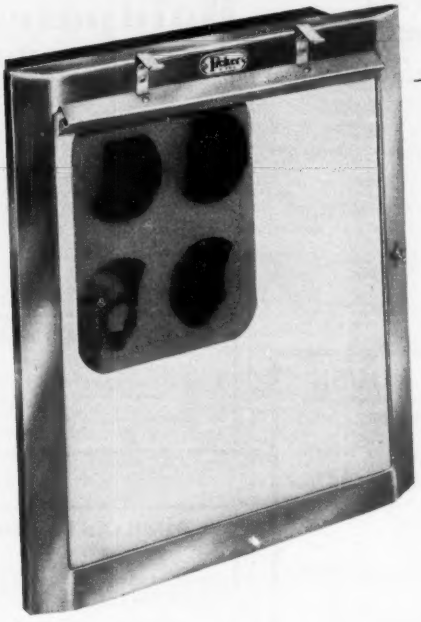

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NOTICES (*Concluded from page 656*)

MAY 23. School Physicians' Association. Page 614, issue of April 19.
MAY 24–26. American Goiter Association. Page 384, issue of March 8.
JUNE 7–9. American Radium Society. Page 656.
JUNE 7–10. American College of Chest Physicians. Page 494, issue of March 29.
JUNE 9 AND 10. American Society for the Study of Sterility. Page 274, issue of February 15.
JUNE 11–15. American Medical Association. Annual Session. Atlantic City, New Jersey.
JUNE 11–15. Physicians' Art Exhibit at A.M.A. Meeting. Page 614, issue of April 19.
JUNE 15–17. American Electroencephalographic Society. Page 346, issue of March 1.
JUNE 18–20. American Neurological Association. Page 614, issue of April 19.
JUNE 20–23. American Orthopaedic Association. Page 422, issue of March 15.
SEPTEMBER 4–8. American Congress of Physical Medicine. Page 238, issue of February 8.
SEPTEMBER 19. American Medical Writers' Association. Page 1066, issue of December 28.
SEPTEMBER 19–21. Mississippi Valley Medical Society. Page 1066, issue of December 28.
SEPTEMBER 30–OCTOBER 2. New Hampshire Medical Society. Annual Meeting. Equinox House, Manchester, Vermont.
OCTOBER 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.
NOVEMBER 10–21. Pan-Pacific Surgical Association. Page 680, issue of October 26.
JULY 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

DISTRICT MEDICAL SOCIETIES

HAMPDEN

MAY 1. 6:00 p.m. Annual meeting. Hotel Kimball, Springfield.

HAMPSHIRE

MAY 2. 4:30 p.m. Annual meeting. Jones Library, Amherst.

NORFOLK

MAY 9. Annual dinner.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 3

THURSDAY, MAY 3

*9:00–10:00 a.m. Grand rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Cardiac grand rounds. Main Amphitheatre, Children's Medical Center.
*9:00–11:00 a.m. Medical grand rounds. Joseph H. Pratt Diagnostic Hospital.
7:15 p.m. Clinical conference and staff meeting. Conference room, New England Hospital.

FRIDAY, MAY 4

*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined medical and surgical staff rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical clinic. South End Health Unit, 57 East Concord Street, Boston.
10:00 a.m. Boston University School of Medicine Alumni Association. Auditorium.
*12:00 m.–1:00 p.m. Clinical conference. Dowling Amphitheatre, Boston City Hospital.
*1:30 p.m. Tumor clinic. Outpatient Department, Mount Auburn Hospital, Cambridge.

SATURDAY, MAY 5

*9:00–10:00 a.m. Surgical grand rounds. Joseph H. Pratt Diagnostic Hospital.
All-day scientific meeting. Boston Dispensary. Hotel Kenmore, Boston.

MONDAY, MAY 7

*11:30 a.m.–12:15 p.m. Clinical conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological conference. Main Amphitheatre, Peter Bent Brigham Hospital.

TUESDAY, MAY 8

*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
8:00 p.m. Harvard Medical Society. Amphitheatre, Building D, Harvard Medical School.

WEDNESDAY, MAY 9

*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical clinic, including psychiatric conferences. (Children's Medical Center.) Amphitheatre, Children's Hospital.
*12:00 m. Clinicopathological conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological conference. (Children's Medical Center.) Amphitheatre, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined clinic of all services. (Children's Medical Center.) Amphitheatre, Children's Hospital.

*Open to the medical profession.

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